

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/EP05/001465

International filing date: 14 February 2005 (14.02.2005)

Document type: Certified copy of priority document

Document details: Country/Office: EP
Number: 04021974.3
Filing date: 16 September 2004 (16.09.2004)

Date of receipt at the International Bureau: 05 April 2005 (05.04.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse



**Europäisches
Patentamt**

**European
Patent Office**

**Office européen
des brevets**

Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

04021974.3

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk



Anmeldung Nr:
Application no.: 04021974.3
Demande no:

Anmeldetag:
Date of filing: 16.09.04
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

Laboratorios Dr. Esteve S.A.
Av. Mare de Déu de Montserrat, 221
08041 Barcelona
ESPAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Substituted pyrazoline compounds, their preparation and use as medicaments

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)
revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D231/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
PL PT RO SE SI SK TR LI

ESTA-0423
16.09.2004

Substituted pyrazoline compounds, their preparation and use as medicaments

The present invention relates to substituted pyrazoline compounds, methods for their preparation, medicaments comprising these compounds as well as their use for the preparation of a medicament for the treatment of humans and animals.

Triglycerides are the chemical form in which most fat exists in food as well as in the body. Triglycerides are present in blood plasma and, in association with cholesterol, form the plasma lipids. Triglycerides in blood plasma are derived from fats consumed directly or are synthesized from e.g. carbohydrates. Superfluous food intake is converted to triglycerides and transported to fat cells to be stored. Elevated triglycerides may also be a consequence of disease states, such as untreated diabetes mellitus. Excess of triglycerides in plasma (hypertriglyceridemia) is linked to the occurrence of coronary artery disease and possibly other disorders.

Therefore, compounds, which have an effect on triglycerides, especially in blood plasma are useful in the prevention and/or treatment of related disorders.

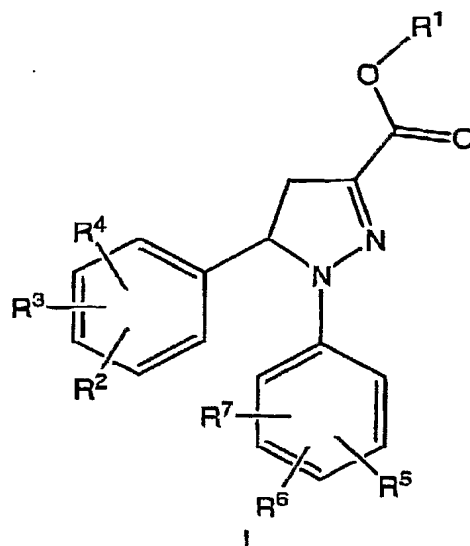
Thus, it was an object of the present invention to provide novel compounds for use as active substances in medicaments, which are suitable for the regulation especially the reduction of triglyceride levels in the blood plasma.

Said object was achieved by providing the substituted pyrazoline compounds of general formula I given below, their stereoisomers, corresponding salts and corresponding solvates thereof.

It has been found that these compounds have a marked effect on the level of triglycerides in the blood plasma.

Thus, in one of its aspects the present invention relates to substituted pyrazoline compounds of general formula

ESTA-0423
16.09.2004



wherein

R^1 represents hydrogen or a linear or branched C_{1-4} -alkyl group,

R^2 , R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R^8$, SH , SR^8 , SOR^8 , SO_2R^8 , NH_2 , NHR^8 , NR^8R^9 , $-(C=O)-NH_2$, $-(C=O)-NHR^8$ or $-(C=O)-NR^8R^9$ whereby R^8 and R^9 for each substituent independently represent linear or branched C_{1-6} alkyl,

R^5 and R^6 independently of each other represent a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R^{10}$, SH , SR^{10} , SOR^{10} , NH_2 , NHR^{10} , $NR^{10}R^{11}$, $-(C=O)-NH_2$, $-(C=O)-NHR^{10}$ and $-(C=O)-NR^{10}R^{11}$, whereby R^{10} and

ESTA-0423
16.09.2004

optionally R^{11} for each substituent independently represent linear or branched C_{1-6} alkyl;

R^7 represents hydrogen, a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R^{10}$, SH , SR^{10} , SOR^{10} , NH_2 , NHR^{10} , $NR^{10}R^{11}$, $-(C=O)-NH_2$, $-(C=O)-NHR^{10}$ and $-(C=O)-NR^{10}R^{11}$, whereby R^{10} and optionally R^{11} for each substituent independently represent linear or branched C_{1-6} alkyl;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

It is very preferred if to these compounds according to formula I the following proviso applies:

with the proviso that

if R^1 and R^7 are H and R^5 and R^6 both represent Cl in the 3- and 4-position of the phenyl ring neither of R^2 , R^3 and R^4 may represent F in the 4-position of the phenyl ring if the other two of R^2 , R^3 and R^4 both represent H.

These compounds had a surprising effect on the blood levels of diet relevant substances, e.g. Triglycerides.

As a general remark the claim to the compounds will cover as well any prodrug of the claimed and invented compounds as well as any use thereof especially including their esters and ethers. Examples of well known methods of producing a prodrug of a given acting compound are known to those skilled in the art and can be found e.g. in Krogsgaard-Larsen et al., Textbook of Drugdesign and Discovery, Taylor & Francis (April 2002).

Preferred linear or branched, saturated or unsaturated aliphatic groups, which may be substituted by one or more substituents, may preferably be selected from the

ESTA-0423
16.09.2004

group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, vinyl, ethinyl, propenyl, propinyl, butenyl and butinyl.

In the context of this invention, alkyl and cycloalkyl radicals are understood as meaning saturated and unsaturated (but not aromatic), branched, unbranched and cyclic hydrocarbons, which can be unsubstituted or mono- or polysubstituted. In these radicals, C₁₋₂-alkyl represents C1- or C2-alkyl, C₁₋₃-alkyl represents C1-, C2- or C3-alkyl, C₁₋₄-alkyl represents C1-, C2-, C3- or C4-alkyl, C₁₋₅-alkyl represents C1-, C2-, C3-, C4-, or C5-alkyl, C₁₋₆-alkyl represents C1-, C2-, C3-, C4-, C5- or C6-alkyl, C₁₋₇-alkyl represents C1-, C2-, C3-, C4-, C5-, C6- or C7-alkyl, C₁₋₈-alkyl represents C1-, C2-, C3-, C4-, C5-, C6-, C7- or C8-alkyl, C₁₋₁₀-alkyl represents C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8-, C9- or C10-alkyl and C₁₋₁₈-alkyl represents C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8-, C9-, C10-, C11-, C12-, C13-, C14-, C15-, C16-, C17- or C18-alkyl. Furthermore, C₃₋₄-cycloalkyl represents C3- or C4-cycloalkyl, C₃₋₅-cycloalkyl represents C3-, C4- or C5-cycloalkyl, C₃₋₆-cycloalkyl represents C3-, C4-, C5- or C6-cycloalkyl, C₃₋₇-cycloalkyl represents C3-, C4-, C5-, C6- or C7-cycloalkyl, C₃₋₈-cycloalkyl represents C3-, C4-, C5-, C6-, C7- or C8-cycloalkyl, C₄₋₅-cycloalkyl represents C4- or C5-cycloalkyl, C₄₋₆-cycloalkyl represents C4-, C5- or C6-cycloalkyl, C₄₋₇-cycloalkyl represents C4-, C5-, C6- or C7-cycloalkyl, C₅₋₆-cycloalkyl represents C5- or C6-cycloalkyl and C₅₋₇-cycloalkyl represents C5-, C6- or C7-cycloalkyl. In respect of cycloalkyl, the term also includes saturated cycloalkyls in which one or 2 carbon atoms are replaced by a heteroatom, S, N or O. However, mono- or polyunsaturated, preferably monounsaturated, cycloalkyls without a heteroatom in the ring also in particular fall under the term cycloalkyl as long as the cycloalkyl is not an aromatic system. The alkyl and cycloalkyl radicals are preferably methyl, ethyl, vinyl (ethenyl), propyl, allyl (2-propenyl), 1-propinyl, methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, hexyl, 1-methylpentyl, cyclopropyl, 2-methylcyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cycloheptyl, cyclooctyl, and also adamantyl, (if substituted also CHF₂, CF₃ or CH₂OH) as well as pyrazolinone, oxopyrazolinone, [1,4]-dioxane or dioxolane.

ESTA-0423
16.09.2004

Here, in connection with alkyl and cycloalkyl - unless expressly defined otherwise - the term substituted in the context of this invention is understood as meaning replacement of at least one hydrogen radical by F, Cl, Br, I, NH₂, SH or OH, "polysubstituted" radicals being understood as meaning that the replacement takes effect both on different and on the same atoms several times with the same or different substituents, for example three times on the same C atom, as in the case of CF₃, or at different places, as in the case of -CH(OH)-CH=CH-CHCl₂. Particularly preferred substituents here are F, Cl and OH. In respect of cycloalkyl, the hydrogen radical can also be replaced by OC₁₋₃-alkyl or C₁₋₃-alkyl (in each case mono- or polysubstituted or unsubstituted), in particular methyl, ethyl, n-propyl, i-propyl, CF₃, methoxy or ethoxy.

The term (CH₂)₃₋₈ is to be understood as meaning -CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-CH₂- and -CH₂-CH₂-CH₂-CH₂-CH₂-CH₂-, (CH₂)₁₋₄ is to be understood as meaning -CH₂-, -CH₂-CH₂-, -CH₂-CH₂-CH₂- and -CH₂-CH₂-CH₂-CH₂-, (CH₂)₄₋₅ is to be understood as meaning -CH₂-CH₂-CH₂-CH₂- and -CH₂-CH₂-CH₂-CH₂-CH₂-, etc.

An aryl radical is understood as meaning ring systems with at least one aromatic ring but without heteroatoms even in only one of the rings. Examples are phenyl, naphthyl, fluoranthenyl, fluorenyl, tetralinyl or indanyl, in particular 9H-fluorenyl or anthracenyl radicals, which can be unsubstituted or monosubstituted or polysubstituted.

A heteroaryl radical is understood as meaning heterocyclic ring systems which have at least one unsaturated ring and can contain one or more heteroatoms from the group consisting of nitrogen, oxygen and/or sulfur and can also be mono- or polysubstituted. Examples which may be mentioned from the group of heteroaryls are furan, benzofuran, thiophene, benzothiophene, pyrrole, pyridine, pyrimidine, pyrazine, quinoline, isoquinoline, phthalazine, benzo-1,2,5-thiadiazole, benzothiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole and quinazoline.

Here, in connection with aryl and heteroaryl, substituted is understood as meaning

ESTA-0423

16.09.2004

substitution of the aryl or heteroaryl by R, OR, a halogen, preferably F and/or Cl, a CF_3 , a CN, an NO_2 , an NRR, a C_{1-6} -alkyl (saturated), a C_{1-6} -alkoxy, a C_{3-8} -cycloalkoxy, a C_{3-8} -cycloalkyl or a C_{2-6} -alkylene.

The term "salt" is to be understood as meaning any form of the active compound used according to the invention in which it assumes an ionic form or is charged and is coupled with a counter-ion (a cation or anion) or is in solution. By this are also to be understood complexes of the active compound with other molecules and ions, in particular complexes which are complexed via ionic interactions.

The term "physiologically acceptable salt" means in the context of this invention any salt that is physiologically tolerated (most of the time meaning not being toxic- especially not caused by the counter-ion) if used appropriately for a treatment especially if used on or applied to humans and/or mammals.

These physiologically acceptable salts can be formed with cations or bases and in the context of this invention is understood as meaning salts of at least one of the compounds used according to the invention - usually a (deprotonated) acid - as an anion with at least one, preferably inorganic, cation which is physiologically tolerated - especially if used on humans and/or mammals. The salts of the alkali metals and alkaline earth metals are particularly preferred, and also those with NH_4 , but in particular (mono)- or (di)sodium, (mono)- or (di)potassium, magnesium or calcium salts.

These physiologically acceptable salts can also be formed with anions or acids in the context of this invention is understood as meaning salts of at least one of the compounds used according to the invention - usually protonated, for example on the nitrogen - as the cation with at least one anion which are physiologically tolerated - especially if used on humans and/or mammals. By this is understood in particular, in the context of this invention, the salt formed with a physiologically tolerated acid, that is to say salts of the particular active compound with inorganic or organic acids which are physiologically tolerated - especially if used on humans and/or mammals.

Examples of physiologically tolerated salts of particular acids are salts of:

hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid,

ESTA-0423
16.09.2004

acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid or citric acid.

The term "solvate" according to this invention is to be understood as meaning any form of the active compound according to the invention in which this compound has attached to it via non-covalent binding another molecule (most likely a polar solvent) especially including hydrates and alcoholates, e.g. methanolate.

Unless otherwise stated, the compounds of the invention are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C - or ^{14}C -enriched carbon or ^{15}N -enriched nitrogen are within the scope of this invention.

In a preferred embodiment of the invention for a compound according to formula I at least one of R^2 , R^3 or R^4 represents hydrogen, while at least one of R^2 , R^3 or R^4 is different from hydrogen.

In a preferred embodiment of the invention for a compound according to formula I R^7 represents hydrogen.

In a preferred embodiment of the invention for a compound according to formula I R^2 , R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^2 , R^3 and R^4 independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .

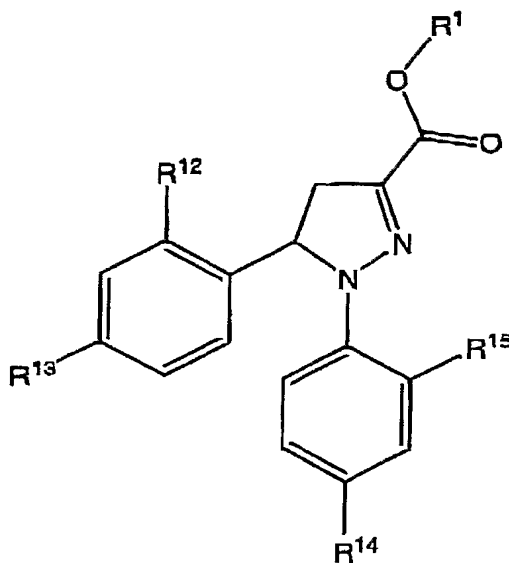
In a preferred embodiment of the invention for a compound according to formula I R^5 and R^6 independently of each other represent a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^5 and R^6 independently of each other represent methyl, ethyl, F, Cl, Br and CF_3 .

ESTA-0423
16.09.2004

In a preferred embodiment of the invention for a compound according to formula I R^2 represents a chlorine atom in the 4-position of the phenyl ring, while R^3 and R^4 represent hydrogen.

In a preferred embodiment of the invention for a compound according to formula I R^5 and R^6 each represent a chlorine atoms in the 2- and 4-position of the phenyl ring, while R^7 represents hydrogen.

In a preferred embodiment of the invention for a compound according to formula I R^1 represents hydrogen, methyl or ethyl, preferably hydrogen.



II

In a highly preferred further aspect of the invention the compound of general formula I is represented by a compound of general formula II

wherein

R^1 represents hydrogen or a linear or branched C_{1-4} -alkyl group,

ESTA-0423
16.09.2004

R^{12} or R^{13} independently of each other represent a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , SH , NH_2 , hydrogen, methyl, ethyl, F , Cl , Br and CF_3 .

R^{14} or R^{15} independently of each other represent a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , SH , NH_2 , methyl, ethyl, F , Cl , Br and CF_3 .

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

In a preferred embodiment of the invention for a compound according to formula II R^{12} and R^{13} independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^{12} and R^{13} independently of each other represent hydrogen, methyl, ethyl, F , Cl , Br and CF_3 .

In a preferred embodiment of the invention for a compound according to formula II R^{14} , and R^{15} independently of each other represent a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^{14} and R^{15} independently of each other represent methyl, ethyl, F , Cl , Br and CF_3 .

In a preferred embodiment of the invention for a compound according to formula II R^{13} represents Cl and R^{12} represents hydrogen.

In a preferred embodiment of the invention for a compound according to formula II R^{14} and R^{15} each represent Cl .

In a preferred embodiment of the invention for a compound according to formula II R^1 represents hydrogen, methyl or ethyl, preferably hydrogen.

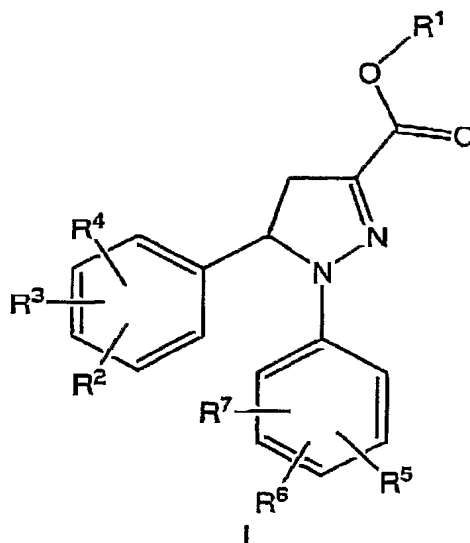
ESTA-0423
16.09.2004

In another preferred embodiment the compound according to formula I or II is selected from the group consisting of:

5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,

optionally in the form of a corresponding N-oxide, a corresponding salt or a corresponding solvate.

Another aspect of the invention is a combination of compounds comprising at least one substituted pyrazoline compound of general formula I



wherein

R¹ represents hydrogen or a linear or branched C₁₋₄-alkyl group,

R², R³ and R⁴ independently of each other represent hydrogen, a linear or branched C₁₋₆-alkyl group, a linear or branched C₁₋₆-alkoxy group, a halogen atom, CH₂F, CHF₂, CF₃, CN, OH, NO₂, -(C=O)-R⁸, SH, SR⁸, SOR⁸, SO₂R⁸, NH₂, NHR⁸, NR⁸R⁹, -(C=O)-NH₂, -(C=O)-NHR⁸ or -(C=O)-NR⁸R⁹ whereby R⁸

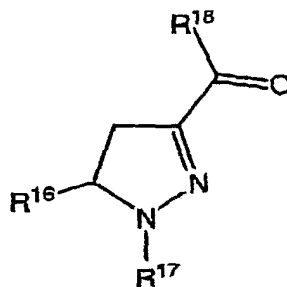
ESTA-0423
16.09.2004

and R^9 for each substituent independently represent linear or branched C_{1-6} alkyl,

R^5 , R^6 and R^7 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R^{10}$, SH , SR^{10} , SOR^{10} , NH_2 , NHR^{10} , $NR^{10}R^{11}$, $-(C=O)-NH_2$, $-(C=O)-NHR^{10}$ and $-(C=O)-NR^{10}R^{11}$, whereby R^{10} and optionally R^{11} for each substituent independently represent linear or branched C_{1-6} alkyl;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof;

and at least one substituted pyrazoline compound of general formula X



X

wherein

R^{16} represents an optionally at least mono-substituted phenyl group,

R^{17} represents an optionally at least mono-substituted phenyl group,

ESTA-0423
16.09.2004

R^{18} represents a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an $-NR^{19}R^{20}$ -moiety,

R^{19} and R^{20} , identical or different, represent a hydrogen atom, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system and/or bonded via a linear or branched alkylene group, an $-SO_2-R^{21}$ -moiety, or an $-NR^{22}R^{23}$ -moiety, with the proviso that R^{19} and R^{20} do not identically represent hydrogen,

R^{21} represents a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic group, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with a mono- or polycyclic ring-system, or an optionally at least mono-substituted aryl or heteroaryl group, which may be condensed with a mono- or polycyclic ring system and/or bonded via a linear or branched alkylene group,

R^{22} and R^{23} , identical or different, represent a hydrogen atom, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least

ESTA-0423
16.09.2004

mono-substituted aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system and/or bonded via a linear or branched alkylene group,

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula I at least one of R^2 , R^3 or R^4 represents hydrogen, while at least one of R^2 , R^3 or R^4 is different from hydrogen.

In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula I at least one of R^5 , R^6 or R^7 represents hydrogen, while at least one R^5 , R^6 or R^7 is different from hydrogen.

In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula I R^2 , R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^2 , R^3 and R^4 independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .

In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula I R^5 , R^6 and R^7 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^5 , R^6 and R^7 independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .

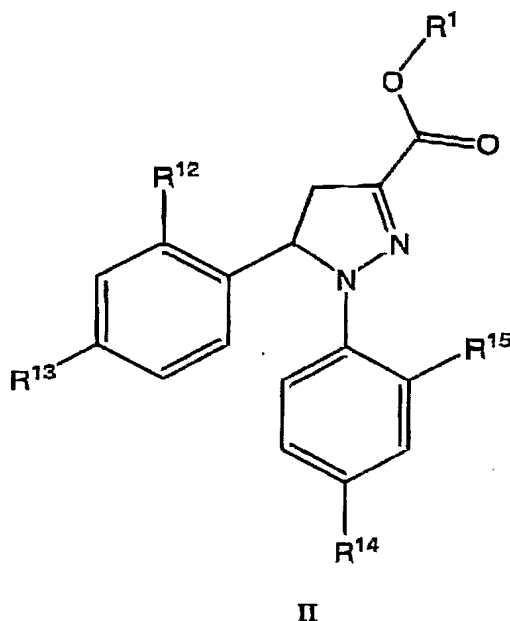
In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula I R^2 represents a chlorine atom in the 4-position of the phenyl ring, while R^3 and R^4 represent hydrogen.

ESTA-0423
16.09.2004

In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula I R^5 and R^6 each represent a chlorine atom in the 2- and 4-position of the phenyl ring, while R^7 represents hydrogen.

In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula I R^1 represents hydrogen, methyl or ethyl, preferably hydrogen.

In a preferred embodiment of the combination of compounds according to the invention the compound of general formula I is represented by a compound of general formula II



wherein

R^1 represents hydrogen or a linear or branched C_{1-4} -alkyl group,

R^{12} , R^{13} , R^{14} or R^{15} independently of each other represent a linear or branched C_{1-8} -alkyl group, a linear or branched C_{1-8} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , SH , NH_2 , hydrogen, methyl, ethyl, F , Cl , Br and CF_3 ,

ESTA-0423
16.09.2004

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula II R^{12} and R^{13} independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^{12} and R^{13} independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .

In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula II R^{14} , and R^{15} independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^{14} and R^{15} independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .

In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula II R^{13} represents Cl and R^{12} represents hydrogen.

In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula II R^{14} and R^{15} each represent Cl.

In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula II R^1 represents hydrogen, methyl or ethyl, preferably hydrogen.

In a preferred embodiment of the combination of compounds according to the invention the compound according to formula I or II is selected from the group consisting of:

ESTA-0423

16.09.2004

5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,

optionally in the form of a corresponding N-oxide, a corresponding salt or a corresponding solvate.

In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula X R^{16} represents a phenyl group, which is optionally substituted by one or more substituents independently selected from the group consisting of a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R'$, SH , SR' , SOR' , SO_2R' , NH_2 , NHR' , $NR'R''$, $-(C=O)-NH_2$, $-(C=O)-NHR'$ and $-(C=O)-NR'R''$ whereby R' and R'' for each substituent independently represent linear or branched C_{1-6} alkyl, preferably R^{16} represents a phenyl group, which is optionally substituted by one or more substituents selected from the group consisting of methyl, ethyl, F , Cl , Br and CF_3 , more preferably R^{16} represents a phenyl group, which is mono-substituted with a chlorine atom in the 4-position.

In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula X R^{17} represents a phenyl group, which is optionally substituted by one or more substituents independently selected from the group consisting of a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R'$, SH , SR' , SOR' , SO_2R' , NH_2 , NHR' , $NR'R''$, $-(C=O)-NH_2$, $-(C=O)-NHR'$ and $-(C=O)-NR'R''$, whereby R' and optionally R'' for each substituent independently represent linear or branched C_{1-6} alkyl, preferably R^{17} represents a phenyl group, which is optionally substituted by one or more substituents independently selected from the group consisting of methyl, ethyl, F , Cl , Br and CF_3 , more preferably R^{17} represents a phenyl group, which is di-substituted with two chlorine atoms in its 2- and 4-position.

In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula X R^{18} represents a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom

ESTA-0423

16.09.2004

as ring member containing C_{3-8} cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted, 5- or 6-membered aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an $-NR^{18}R^{20}$ -moiety, preferably R^{18} represents a saturated, optionally at least mono-substituted, optionally one or more nitrogen-atoms as ring member containing C_{3-8} cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an $-NR^{19}R^{20}$ -moiety, more preferably R^{19} represents a pyrrolidinyl group, a piperidinyl group or a piperazinyl group, whereby each of these groups may be substituted with one or more C_{1-6} -alkyl groups, or an $-NR^{18}R^{19}$ -moiety.

In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula X R^{19} and R^{20} , identical or different, represent a hydrogen atom, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted C_{1-6} -aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing C_{3-8} -cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted, 5- or 6-membered aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system and/or bonded via a methylene ($-CH_2-$) or ethylene ($-CH_2-CH_2-$)-group, an $-SO_2-R^{21}$ -moiety, or an $-NR^{22}R^{23}$ -moiety, preferably one of these residues R^{19} and R^{20} represents a hydrogen atom and the other one of these residues R^{19} and R^{20} represents a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing C_{3-8} -cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted, 5- or 6-membered aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, an $-SO_2-R^{21}$ -moiety, or an $-NR^{22}R^{23}$ -moiety, or R^{19} and R^{20} , identical or different, each represent a C_{1-6} alkyl group, more preferably one of these residues R^{19} and R^{20} represents a hydrogen atom and the other one of these residues R^{19} and R^{20} represents an optionally at least mono-substituted pyrrolidinyl group, an optionally at least mono-substituted piperidinyl

ESTA-0423
16.09.2004

group, an optionally at least mono-substituted piperazinyl group, an optionally at least mono-substituted triazolyl group, an $-\text{SO}_2\text{-R}^{21}$ -moiety, or an $-\text{NR}^{22}\text{R}^{23}$ -moiety, or R^{19} and R^{20} , identical or different, represent a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, a sec-butyl group or a tert.-butyl group.

In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula X R^{21} represents a linear or branched, saturated or unsaturated, optionally at least mono-substituted C_{1-6} aliphatic group, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing C_{3-8} cycloaliphatic group, which may be condensed with a mono- or polycyclic ring-system, or an optionally at least mono-substituted, 5- or 6-membered aryl or heteroaryl group, which may be condensed with a mono- or polycyclic ring system and/or bonded via a methylene ($-\text{CH}_2-$) or ethylene ($-\text{CH}_2\text{-CH}_2-$)-group, preferably R^{21} represents a C_{1-6} -alkyl group, a saturated, optionally at least mono-substituted cycloaliphatic group, which may be condensed with a mono- or polycyclic ring-system, or a phenyl group, which is optionally substituted with one or more C_{1-6} alkyl groups.

In a preferred embodiment of the combination of compounds according to the invention for a compound according to formula X R^{22} and R^{23} , identical or different, represent a hydrogen atom, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted C_{1-6} aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing C_{3-8} cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted, 5- or 6 membered aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system and/or bonded via a methylene ($-\text{CH}_2-$) or ethylene ($-\text{CH}_2\text{-CH}_2-$)-group, preferably R^{22} and R^{23} , identical or different, represent a hydrogen atom or a C_{1-6} alkyl radical.

In a preferred embodiment of the combination of compounds according to the invention the compound according to general formula X is represented by a structure wherein

ESTA-0423
16.09.2004

R^{16} represents a phenyl ring, which is mono-substituted with a halogen atom, preferably a chlorine atom, in its 4-position,

R^{17} represents a phenyl ring, which is di-substituted with two halogen atoms, preferably chlorine atoms, in its 2- and 4-position,

R^{18} represents a pyrrolidinyl group, a piperidinyl group, a piperazinyl group, a homo-piperazinyl group, a morpholinyl group, or an $-NR^{19}R^{20}$ -moiety,

R^{19} represents a hydrogen atom or a linear or branched C_{1-6} -alkyl group,

R^{20} represents a linear or branched C_{1-6} alkyl group, an $-SO_2-R^{21}$ -moiety, a pyrrolidinyl group, a piperidinyl group, a piperazinyl group, a homo-piperazinyl group, a morpholinyl group, a triazolyl group, whereby each of the heterocyclic rings may be substituted with one or more, identical or different, C_{1-6} -alkyl groups, and

R^{21} represents a phenyl group, which is optionally substituted with one or more C_{1-6} alkyl groups, which may be identical or different,

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

In a preferred embodiment of the combination of compounds according to the invention the combination of compounds comprises at least one compound according to formula X selected from the group consisting of:

N-piperidinyl-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxamide,

ESTA-0423
16.09.2004

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid-[1,2,4]-triazole-4-yl-amide,

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid-(4-methyl-piperazin-1-yl)-amide,

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid diethylamide,

[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-yl]-piperidine-1-yl-methanone,

N-[5-(4-Chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazole-3-carbonyl]-4-methylphenylsulfonamide,

optionally in the form of a corresponding N-oxide, a corresponding salt or a corresponding solvate.

In a preferred embodiment of the combination of compounds according to the invention the combination of compounds comprises at least one compound according to formula X selected from

5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,

and

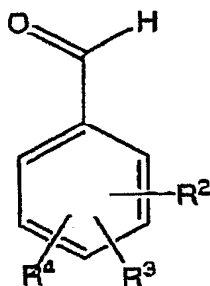
N-piperidinyl-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxamide;

each optionally in the form of a corresponding N-oxide, a corresponding salt or a corresponding solvate.

ESTA-0423

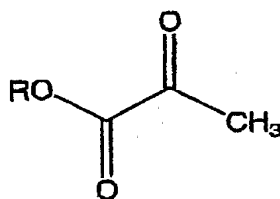
16.09.2004

In another aspect the present invention also provides a process for the preparation of substituted pyrazoline compounds of general formula I or II given above, in that at least one benzaldehyde compound of general formula III



(III)

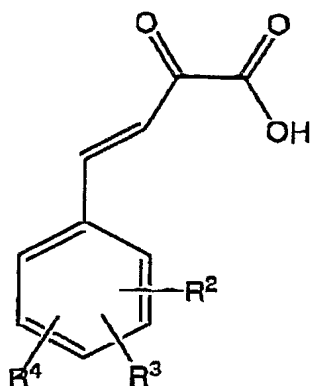
wherein R^2 , R^3 and R^4 have the meaning mentioned above, is reacted with a pyruvate compound of general formula (IV)



(IV),

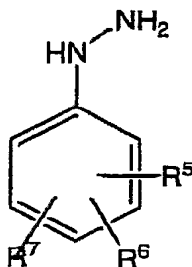
wherein R is a branched or unbranched C_{1-6} alkyl radical, to yield a compound of general formula (V)

ESTA-0423
16.09.2004



(V)

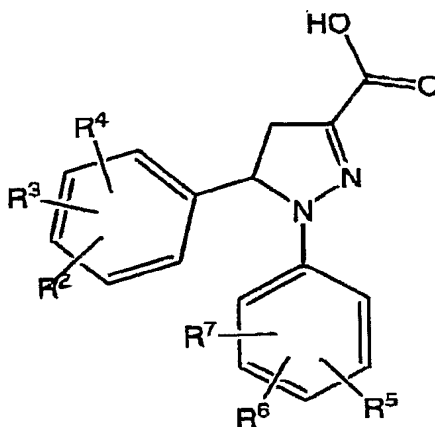
wherein R^1 has the meaning given above, which is optionally isolated and/or optionally purified, and which is reacted with an optionally substituted phenyl hydrazine of general formula (VI)



(VI)

or a corresponding salt thereof, wherein R^5 , R^6 and R^7 have the meaning mentioned above, under inert atmosphere, to yield a compound of general formula (VII)

ESTA-0423
16.09.2004



(VII)

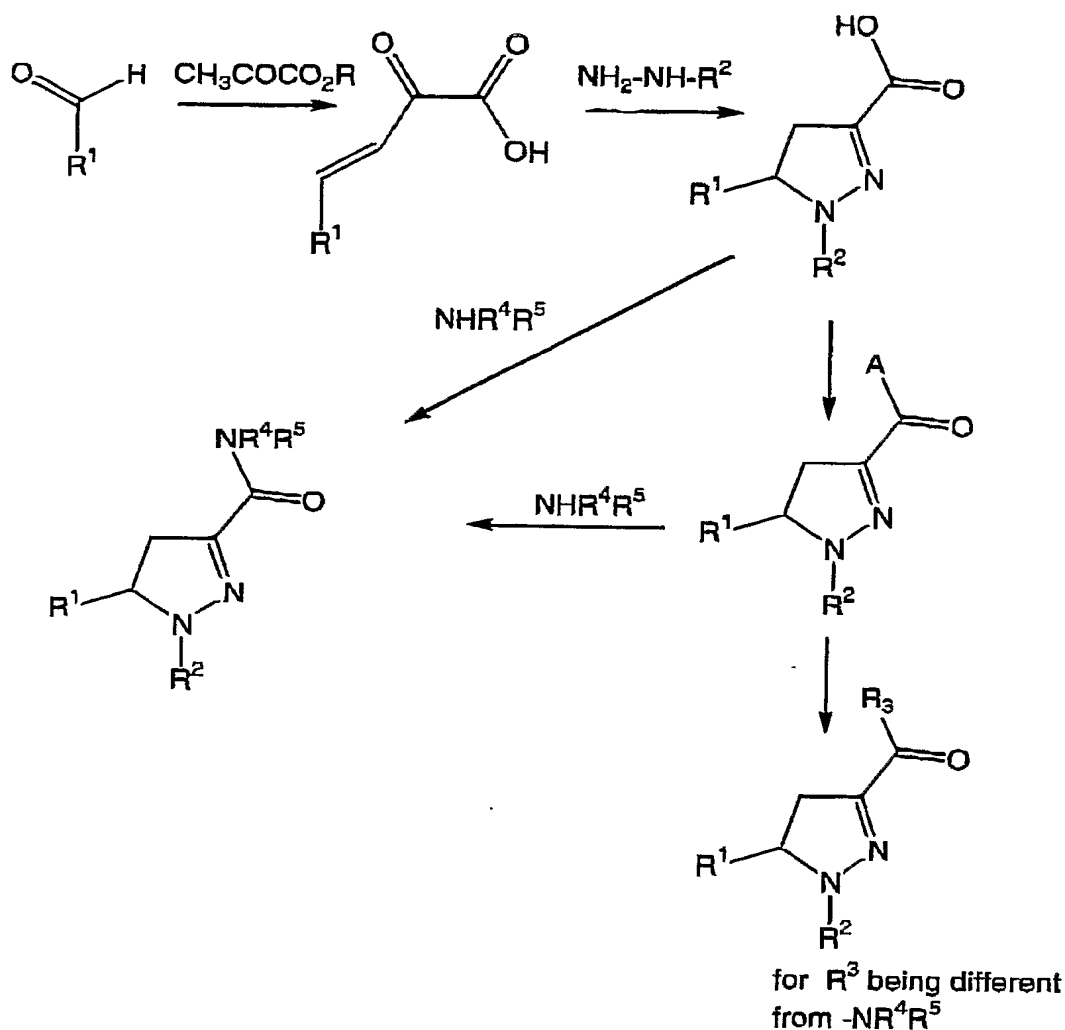
wherein R², R³, R⁴, R⁵, R⁶ and R⁷ have the meaning as given above, which is optionally isolated and/or optionally purified, and optionally esterified to an alkyl-ester if in the substituted pyrazoline compound of general formula I or II according to the invention R¹ is a linear or branched C₁₋₄-alkyl group.

The inventive process is also illustrated in scheme I given below:

ESTA-0423

16.09.2004

Scheme I:



The reaction of the benzaldehyde compound of general formula III with a pyruvate compound of general formula IV is preferably carried out in the presence of at least one base, more preferably in the presence of an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide or an alkali metal methoxide such as sodium methoxide, as described, for example, in Synthetic communications, 26(11), 2229-33, (1996). The respective description is hereby incorporated by reference and forms part of the disclosure. Preferably said reaction is carried out in a protic reaction medium such as a C_{1-4} alkyl alcohol or mixtures of these.

ESTA-0423
16.09.2004

Reaction temperature as well as the duration of the reaction may vary over a broad range. Preferred reaction temperatures range from -10°C to the boiling point of the reaction medium. Suitable reaction times may vary for example from several minutes to several hours.

Also preferred the reaction of the benzaldehyde compound of general formula III with a pyruvate compound of general formula IV is carried out under acid catalysed conditions, more preferably by refluxing the mixture in dichloromethane in the presence of copper(II)trifluoromethanesulfonate as described, for example, in Synlett, (1), 147-149, 2001. The respective description is hereby incorporated by reference and forms part of the disclosure.

The reaction of the compound of general formula (V) with an optionally substituted phenyl hydrazin of general formula (VI) is preferably carried out in a suitable reaction medium such as C_{1-4} -alcohols or ethers such as dioxana or tetrahydrofurane or mixtures of at least two of these afore mentioned compounds. Also preferably, said reaction may be carried out in the presence of an acid, whereby the acid may be organic such as acetic acid and/or inorganic such as hydrochloric acid. Furthermore, the reaction may also be carried out in the presence of a base such as piperidine, piperazine, sodium hydroxide, potassium hydroxide, sodium methoxide or sodium ethoxide, or a mixture of at least two of these bases may also be used.

Reaction temperature as well as the duration of the reaction may vary over a broad range. Suitable reaction temperatures range from room temperature, i.e. approximately 25°C to the boiling point of the reaction medium. Suitable reaction times may vary for example from several minutes to several hours.

The carboxylic group of the compound of general formula (VII) may be activated for further reactions by the introduction of a suitable leaving group according to conventional methods well known to those skilled in the art. Preferably the compounds of general formula (VII) are transferred into an acid chloride, an acid anhydride, a mixed anhydride, a C_{1-4} alkyl ester, an activated ester such as p-

ESTA-0423

16.09.2004

nitrophenylester. Other well known methods for the activation of acids include the activation with N,N-dicyclohexylcarbodiimide or benzotriazol-N-oxotris(dimethylamino) phosphonium hexafluorophosphate (BOP)).

If said activated compound of general formula (VII) is an acid chloride, it is preferably prepared by reaction of the corresponding acid of general formula (VI) with thionyl chloride or oxalyl chloride, whereby said chlorinating agent is also used as the solvent. Also preferably an additional solvent may be used. Suitable solvents include hydrocarbons such as benzene, toluene or xylene, halogenated hydrocarbons such as dichloromethane, chloroform or carbon tetrachloride, ethers such as diethyl ether, dioxane, tetrahydrofuran or dimethoxyethane. Mixtures of two or more solvents from one class or two or more solvents from different classes may also be used. Preferred reaction temperature range from 0° C to the boiling point of the solvent and reaction times from several minutes to several hours.

If said activated compound of general formula (VII) is a mixed anhydride, said anhydride may preferably be prepared, for example, by reaction of the corresponding acid of general formula (VI) with ethyl chloroformate in the presence of a base such as triethylamine or pyridine, in a suitable solvent.

The reaction of general formula (VII) with a compound of general formula HR^3 to yield compounds of general formula I, wherein R^3 represents an $-NR^4R^5$ moiety is preferably carried out in presence of a base such as triethylamine in a reaction medium such as methylenchloride. The temperature is preferably in the range from 0°C to the boiling point of the reaction medium. The reaction time may vary over a broad range, e.g. from several hours to several days.

The reaction of general formula (VII) with a compound of general formula HR^3 to yield compounds of general formula I, wherein R^3 represents a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted aryl or heteroaryl group,

ESTA-0423
16.09.2004

which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system may be carried out according to conventional methods well known to those skilled in the art, e.g. from Pascual, A., J. Prakt Chem., 1999, 341(7), 695-700; Lin, S. et al., Heterocycles, 2001, 55(2), 265-277; Rao, P. et al., J. Org. Chem., 2000, 65(22), 7323-7344, Pearson D.E and Buehler, C.A., Synthesis, 1972, 533-542 and references cited therein. The respective descriptions are hereby incorporated by reference and form part of the present disclosure.

Preferably said reaction is carried out in the presence of a Lewis acid, which is preferably selected from the group consisting of FeCl_3 , ZnCl_2 and AlCl_3 , in a suitable reaction medium such as toluene, benzene, tetrahydrofurane or similar. The temperature is preferably in the range from 0°C to the boiling point of the reaction medium, more preferably from 15 to 25°C . The reaction time may vary over a broad range, e.g. from several minutes to several hours.

The afore mentioned reactions involving the synthesis of the 4,5-dihydro-pyrazole ring or the reaction of a compound comprising said ring are carried out under an inert atmosphere, preferably nitrogen or argon, to avoid oxidation of the ring-system.

During the processes described above the protection of sensitive groups or of reagents may be necessary and/or desirable. The introduction of conventional protective groups as well as their removal may be performed by methods well-known to those skilled in the art.

If the substituted pyrazoline compounds of general formula I or II themselves are obtained in form of a mixture of stereoisomers, particularly enantiomers or diastereomers, said mixtures may be separated by standard procedures known to those skilled in the art, e.g. chromatographic methods or fractionalized crystallization with chiral reagents. It is also possible to obtain pure stereoisomers via stereoselective synthesis.

ESTA-0423
16.09.2004

In a further aspect the present invention also provides a process for the preparation of salts of substituted pyrazoline compounds of general formula I or II and stereoisomers thereof, wherein at least one compound of general formula I or II having at least one basic group is reacted with at least one inorganic and/or organic acid, preferably in the presence of a suitable reaction medium. Suitable reaction media include, for example, any of the ones given above. Suitable inorganic acids include hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, nitric acid, suitable organic acids are e.g. citric acid, maleic acid, fumaric acid, tartaric acid, or derivatives thereof, p-toluenesulfonic acid, methanesulfonic acid or camphersulfonic acid.

In yet a further aspect the present invention also provides a process for the preparation of salts of substituted pyrazoline compounds of general formula I or II or stereoisomers thereof, wherein at least one compound of general formula I or II having at least one acidic group is reacted with one or more suitable bases, preferably in the presence of a suitable reaction medium. Suitable bases are e.g. hydroxides, carbonates or alkoxides, which include suitable cations, derived e.g. from alkaline metals, alkaline earth metals or organic cations, e.g. $[\text{NH}_n\text{R}_{4-n}]^+$, wherein n is 0, 1, 2, 3 or 4 and R represents a branched or unbranched C_{1-4} -alkyl-radical. Suitable reaction media are, for example, any of the ones given above.

Solvates, preferably hydrates, of the substituted pyrazoline compounds of general formula I or II, of corresponding stereoisomers, of corresponding N-oxides or of corresponding salts thereof may also be obtained by standard procedures known to those skilled in the art.

Substituted pyrazoline compounds of general formula I or II, which comprise nitrogen-atom containing saturated, unsaturated or aromatic rings may also be obtained in the form of their N-oxides by methods well known to those skilled in the art.

The purification and isolation of the inventive substituted pyrazoline compounds of general formula I or II, of a corresponding stereoisomer, or salt, or solvate or any

ESTA-0423
16.09.2004

intermediate thereof may, if required, be carried out by conventional methods known to those skilled in the art, e.g. chromatographic methods or recrystallization.

The substituted pyrazoline compounds of general formula I and II given below, their stereoisomers, corresponding N-oxides, corresponding salts thereof and corresponding solvates are toxicologically acceptable and are therefore suitable as pharmaceutical active substances for the preparation of medicaments.

It has been found that the substituted pyrazoline compounds of general formula (I) and (II) given below, stereoisomers thereof, N-oxides thereof, corresponding salts and corresponding solvates have the property to regulate triglyceride levels in blood plasma.

The combination of compounds comprising substituted pyrazoline compounds of general formula (I) and (II) given below, their stereoisomers, corresponding N-oxides, corresponding salts thereof and corresponding solvates and of substituted pyrazoline compounds of general formula (X) given below, their stereoisomers, corresponding N-oxides, corresponding salts thereof and corresponding solvates are toxicologically acceptable and are therefore suitable as pharmaceutical active substances for the preparation of medicaments.

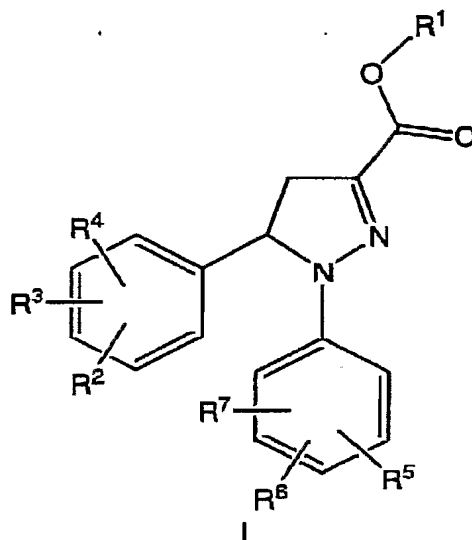
It has been found that the substituted pyrazoline compounds of general formula X given below, stereoisomers thereof, N-oxides thereof, corresponding salts and corresponding solvates have a high affinity to cannabinoid receptors, particularly cannabinoid 1 (CB₁)-receptors, i.e. they act as antagonists on these receptors. In particular these pyrazoline compounds show little or no development of tolerance during treatment particularly with respect to food intake. After ending the treatment with the pyrazoline compounds, reduced increase of body weight is found compared to the pre-treatment level.

Thus, another aspect of the present invention relates to a Medicament comprising at least one substituted pyrazoline compound of general formula I or II according to the invention and optionally one or more pharmaceutically acceptable excipients.

ESTA-0423

16.09.2004

Thus, another aspect of the present invention relates to a Medicament comprising at least one substituted pyrazoline compound of general formula I



wherein

R^1 represents hydrogen or a linear or branched C_{1-4} -alkyl group,

R^2 , R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R^8$, SH , SR^8 , SOR^8 , SO_2R^8 , NH_2 , NHR^8 , NR^8R^9 , $-(C=O)-NH_2$, $-(C=O)-NHR^8$ or $-(C=O)-NR^8R^9$ whereby R^8 and R^9 for each substituent independently represent linear or branched C_{1-6} alkyl,

R^5 , R^6 and R^7 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R^{10}$, SH , SR^{10} , SOR^{10} , NH_2 ,

ESTA-0423
16.09.2004

NHR^{10} , $\text{NR}^{10}\text{R}^{11}$, $-(\text{C}=\text{O})-\text{NH}_2$, $-(\text{C}=\text{O})-\text{NHR}^{10}$ and $-(\text{C}=\text{O})-\text{NR}^{10}\text{R}^{11}$, whereby R^{10} and optionally R^{11} for each substituent independently represent linear or branched C_{1-8} alkyl;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof;

and optionally one or more pharmaceutically acceptable excipients.

In an embodiment of the medicament according to the invention for the compound according to formula I at least one of R^2 , R^3 or R^4 represents hydrogen, while at least one of R^2 , R^3 or R^4 is different from hydrogen.

In an embodiment of the medicament according to the invention for the compound according to formula I at least one of R^5 , R^6 or R^7 represents hydrogen, while at least one R^5 , R^6 or R^7 is different from hydrogen.

In an embodiment of the medicament according to the invention for the compound according to formula I R^2 , R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-8} -alkyl group, a halogen atom, or CF_3 , preferably R^2 , R^3 and R^4 independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .

In an embodiment of the medicament according to the invention for the compound according to formula I R^5 , R^6 and R^7 independently of each other represent hydrogen, a linear or branched C_{1-8} -alkyl group, a halogen atom, or CF_3 , preferably R^5 , R^6 and R^7 independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .

In an embodiment of the medicament according to the invention for the compound according to formula I R^2 represents a chlorine atom in the 4-position of the phenyl ring, while R^3 and R^4 represent hydrogen.

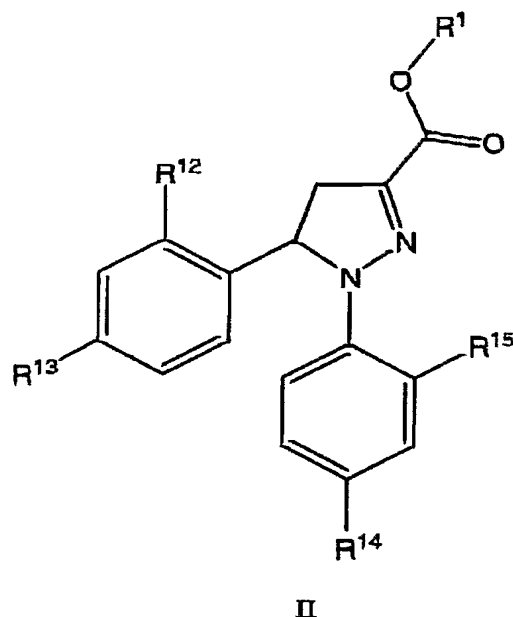
ESTA-0423

16.09.2004

In an embodiment of the medicament according to the invention for the compound according to formula I R^5 and R^6 each represent a chlorine atoms in the 2- and 4-position of the phenyl ring, while R^7 represents hydrogen.

In an embodiment of the medicament according to the invention for the compound according to formula I R^1 represents hydrogen, methyl or ethyl, preferably hydrogen.

In an embodiment of the medicament according to the invention the compound according to formula I is represented by a compound of general formula (II)



wherein

R^1 represents hydrogen or a linear or branched C_{1-4} -alkyl group,

R^{12} , R^{13} , R^{14} or R^{15} independently of each other represent a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , SH , NH_2 , hydrogen, methyl, ethyl, F , Cl , Br and CF_3 .

ESTA-0423
16.09.2004

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

In an embodiment of the medicament according to the invention for the compound according to formula II R^{12} and R^{13} independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^{12} and R^{13} independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .

In an embodiment of the medicament according to the invention for the compound according to formula II R^{14} , and R^{15} independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^{14} and R^{15} independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .

In an embodiment of the medicament according to the invention for the compound according to formula II R^{13} represents Cl and R^{12} represents hydrogen.

In an embodiment of the medicament according to the invention for the compound according to formula II R^{14} and R^{15} each represent Cl.

In an embodiment of the medicament according to the invention for the compound according to formula II R^1 represents hydrogen, methyl or ethyl, preferably hydrogen.

In an embodiment of the medicament according to the invention the compound according to formulas I or II is selected from the group consisting of:

5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,

optionally in the form of a corresponding N-oxide, a corresponding salt or a corresponding solvate.

ESTA-0423
16.09.2004

Another aspect of the invention is a medicament comprising at least one combination of compounds according to the invention and optionally one or more pharmaceutically acceptable excipients.

In an embodiment of the medicaments according to the invention the medicament is for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, preferably bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetes.

In an embodiment of the medicament comprising the compound according to formula I or II according to the invention the medicament is for the prophylaxis and/or treatment of disorders of the central nervous system, disorders of the immune system, disorders of the cardiovascular system, disorders of the endocrinous system, disorders of the respiratory system, disorders of the gastrointestinal tract or reproductive disorders.

In an embodiment of the medicament comprising the combination according to the invention the medicament is for the modulation of cannabinoid-receptors, preferably cannabinoid 1 (CB₁) receptors, for the prophylaxis and/or treatment of disorders of the central nervous system, disorders of the immune system, disorders of the cardiovascular system, disorders of the endocrinous system, disorders of the respiratory system, disorders of the gastrointestinal tract or reproductive disorders.

In an embodiment of the medicaments according to the invention the medicament is for the prophylaxis and/or treatment of food intake disorders, preferably bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity.

In an embodiment of the medicaments according to the invention the medicament is for the prophylaxis and/or treatment of psychosis.

ESTA-0423
16.09.2004

In an embodiment of the medicaments according to the invention the medicament is for the prophylaxis and/or treatment of alcohol abuse and/or addiction, nicotine abuse and/or addiction, drug abuse and/or addiction and/or medicament abuse and/or addiction, preferably drug abuse and/or addiction and/or nicotine abuse and/or addiction.

In an embodiment of the medicaments according to the invention the medicament is for the prophylaxis and/or treatment of one or more disorders selected from the group consisting of schizophrenia, anxiety, depression, epilepsy, neurodegenerative disorders, cerebellar disorders, spinocerebellar disorders, cognitive disorders, cranial trauma, panic attacks, peripheral neuropathy, glaucoma, migraine, Morbus Parkinson, Morbus Huntington, Morbus Alzheimer, Raynaud's disease, tremblement disorders, compulsive disorders, senile dementia, thymic disorders, tardive dyskinesia, bipolar disorders, cancer, medicament-induced movement disorders, dystonia, endotoxemic shock, hemorrhagic shock, hypotension, insomnia, immunologic disorders, sclerotic plaques, vomiting, diarrhea, asthma, memory disorders, pruritus, pain, or for potentiation of the analgesic effect of narcotic and non-narcotic analgesics, or for influencing intestinal transit.

Said medicaments may also comprise any combination of one or more of the substituted pyrazoline compounds of general formula I given above, stereoisomers thereof, corresponding N-oxides thereof, physiologically acceptable salts thereof or physiologically acceptable solvates thereof.

Particularly preferably said medicaments are suitable for the prophylaxis and/or treatment of alcohol abuse, drug abuse and/or medicament abuse, preferably drug abuse and the treatment of obesity.

Medicaments and/or drugs, which are frequently the subject of misuse include opioids, barbiturates, cannabis, cocaine, amphetamines, phencyclidine, hallucinogens and benzodiazepines.

The medicament according to the present invention may be in any form suitable for the application to humans and/or animals, preferably humans including infants,

ESTA-0423

16.09.2004

children and adults and can be produced by standard procedures known to those skilled in the art. The composition of the medicament may vary depending on the route of administration.

The medicament of the present invention may for example be administered parentally in combination with conventional injectable liquid carriers, such as water or suitable alcohols. Conventional pharmaceutical excipients for injection, such as stabilizing agents, solubilizing agents, and buffers, may be included in such injectable compositions. These medicaments may for example be injected intramuscularly, intraperitoneally, or intravenously.

Solid oral compositions (which are preferred as are liquid ones) may be prepared by conventional methods of blending, filling or tableting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are conventional in the art. The tablets may for example be prepared by wet or dry granulation and optionally coated according to the methods well known in normal pharmaceutical practice., in particular with an enteric coating.

The mentioned formulations will be prepared using standard methods such as those described or referred to in the Spanish and US Pharmacopeias and similar reference texts.

Medicaments according to the present invention may also be formulated into orally administrable compositions containing one or more physiologically compatible carriers or excipients, in solid or liquid form. These compositions may contain conventional ingredients such as binding agents, fillers, lubricants, and acceptable wetting agents. The compositions may take any convenient form, such as tablets, pellets, capsules, lozenges, aqueous or oily solutions, suspensions, emulsions, or dry powdered forms suitable for reconstitution with water or other suitable liquid medium before use, for immediate or retarded release.

The liquid oral forms for administration may also contain certain additives such as sweeteners, flavoring, preservatives, and emulsifying agents. Non-aqueous liquid

ESTA-0423
16.09.2004

compositions for oral administration may also be formulated, containing edible oils. Such liquid compositions may be conveniently encapsulated in e.g., gelatin capsules in a unit dosage amount.

The compositions of the present invention may also be administered topically or via a suppository.

The daily dosage for humans and animals may vary depending on factors that have their basis in the respective species or other factors, such as age, sex, weight or degree of illness and so forth. The daily dosage for humans may preferably be in the range from 1 to 2000, preferably 1 to 1500, more preferably 1 to 1000 milligrams of active substance to be administered during one or several intakes per day.

Another preferred aspect of the invention is the use of at least one substituted pyrazoline compound of formula I or II according to the invention or at least one combination of compounds according to the invention (and optionally one or more pharmaceutically acceptable excipients), for the preparation of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetes.

Another preferred aspect of the invention is the use of at least one substituted pyrazoline compound of formula I or II according to the invention (and optionally one or more pharmaceutically acceptable excipients,) for the preparation of a medicament for the prophylaxis and/or treatment of disorders of the central nervous system, disorders of the immune system, disorders of the cardiovascular system, disorders of the endocrinous system, disorders of the respiratory system, disorders of the gastrointestinal tract or reproductive disorders.

Another preferred aspect of the invention is the use of at least one combination of compounds according to the invention (and optionally one or more pharmaceutically acceptable excipients,) for the preparation of a medicament for the modulation of

ESTA-0423
16.09.2004

cannabinoid-receptors, preferably cannabinoid 1 (CB₁) receptors, for the prophylaxis and/or treatment of disorders of the central nervous system, disorders of the immune system, disorders of the cardiovascular system, disorders of the endocrinous system, disorders of the respiratory system, disorders of the gastrointestinal tract or reproductive disorders.

Another preferred aspect of the invention is the use of at least one substituted pyrazoline compound of formula I or II according to the invention or at least one combination of compounds according to the invention (and optionally one or more pharmaceutically acceptable excipients), for the preparation of a medicament for the prophylaxis and/or treatment of food intake disorders, preferably bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity.

Another preferred aspect of the invention is the use of at least one substituted pyrazoline compound of formula I or II according to the invention or at least one combination of compounds according to the invention (and optionally one or more pharmaceutically acceptable excipients), for the preparation of a medicament for the prophylaxis and/or treatment of psychosis.

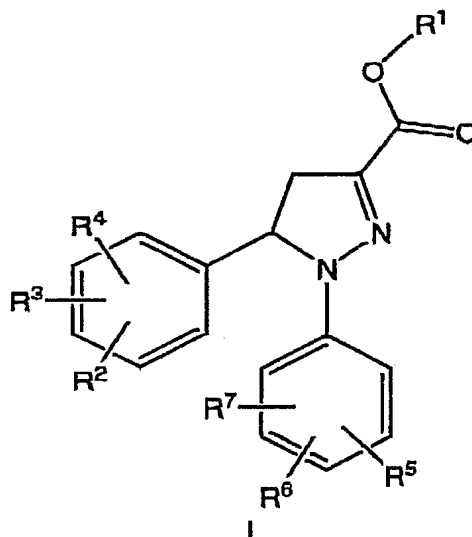
Another preferred aspect of the invention is the use of at least one substituted pyrazoline compound of formula I or II according to the invention or at least one combination of compounds according to the invention (and optionally one or more pharmaceutically acceptable excipients), for the preparation of a medicament for the prophylaxis and/or treatment of alcohol abuse and/or addiction, nicotine abuse and/or addiction, medicament abuse and/or addiction and/or drug abuse and/or addiction, preferably drug abuse and/or addiction or nicotine abuse and/or addiction.

Another preferred aspect of the invention is the use of at least one substituted pyrazoline compound of formula I or II according to the invention or at least one combination of compounds according to the invention (and optionally one or more pharmaceutically acceptable excipients), for the preparation of a medicament for the prophylaxis and/or treatment of one or more disorders selected from the group consisting of schizophrenia, anxiety, depression, epilepsy, neurodegenerative

ESTA-0423
16.09.2004

disorders, cerebellar disorders, spinocerebellar disorders, cognitive disorders, cranial trauma, panic attacks, peripheral neuropathy, glaucoma, migraine, Morbus Parkinson, Morbus Huntington, Morbus Alzheimer, Raynaud's disease, tremblement disorders, compulsive disorders, senile dementia, thymic disorders, tardive dyskinesia, bipolar disorders, cancer, medicament-induced movement disorders, dystonia, endotoxemic shock, hemorrhagic shock, hypotension, insomnia, immunologic disorders, sclerotic plaques, vomiting, diarrhea, asthma, memory disorders, pruritus, pain, or for potentiation of the analgesic effect of narcotic and non-narcotic analgesics, or for influencing intestinal transit.

Another preferred aspect of the invention is the use of at least one substituted pyrazoline compound of general formula I



wherein

R^1 represents hydrogen or a linear or branched C_{1-4} -alkyl group,

R^2 , R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R^B$, SH , SR^B , SOR^B , SO_2R^B ,

ESTA-0423

16.09.2004

NH_2 , NHR^8 , NR^8R^9 , $-(\text{C}=\text{O})-\text{NH}_2$, $-(\text{C}=\text{O})-\text{NHR}^8$ or $-(\text{C}=\text{O})-\text{NR}^8\text{R}^9$ whereby R^8 and R^9 for each substituent independently represent linear or branched C_{1-6} alkyl,

R^5 , R^6 and R^7 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(\text{C}=\text{O})-\text{R}^{10}$, SH , SR^{10} , SOR^{10} , NH_2 , NHR^{10} , $\text{NR}^{10}\text{R}^{11}$, $-(\text{C}=\text{O})-\text{NH}_2$, $-(\text{C}=\text{O})-\text{NHR}^{10}$ and $-(\text{C}=\text{O})-\text{NR}^{10}\text{R}^{11}$, whereby R^{10} and optionally R^{11} for each substituent independently represent linear or branched C_{1-6} alkyl;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof;

and optionally one or more pharmaceutically acceptable excipients, for the preparation of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetes.

Another preferred aspect of the invention is the use for the manufacture of a medicament of at least one substituted pyrazoline compound of formula I for which at least one of R^2 , R^3 or R^4 represents hydrogen, while at least one of R^2 , R^3 or R^4 is different from hydrogen for the manufacture of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetes.

ESTA-0423
16.09.2004

Another preferred aspect of the invention is the use of at least one substituted pyrazoline compound of formula I for which at least one of R^5 , R^6 or R^7 represents hydrogen, while at least one R^5 , R^6 or R^7 is different from hydrogen for the manufacture of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetes.

Another preferred aspect of the invention is the use of at least one substituted pyrazoline compound of formula I for which R^2 , R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^2 , R^3 and R^4 independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 for the manufacture of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetes.

Another preferred aspect of the invention is the use of at least one substituted pyrazoline compound of formula I for which R^5 , R^6 and R^7 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^5 , R^6 and R^7 independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 for the manufacture of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetes.

ESTA-0423

16.09.2004

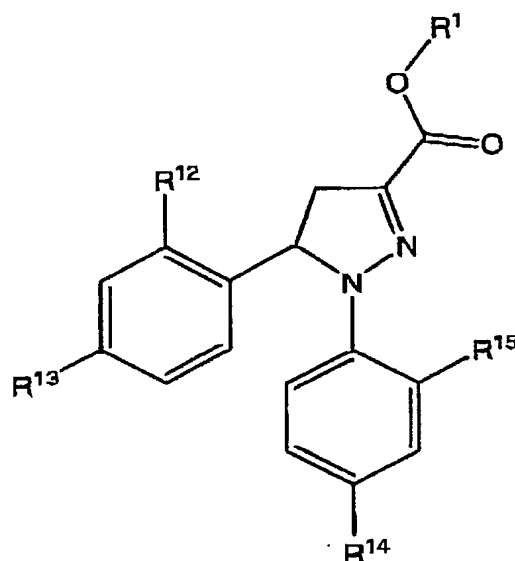
Another preferred aspect of the invention is the use of at least one substituted pyrazoline compound of formula I for which R^2 represents a chlorine atom in the 4-position of the phenyl ring, while R^3 and R^4 represent hydrogen for the manufacture of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetes.

Another preferred aspect of the invention is the use of at least one substituted pyrazoline compound of formula I for which R^5 and R^6 each represent a chlorine atoms in the 2- and 4-position of the phenyl ring, while R^7 represents hydrogen for the manufacture of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetes.

Another preferred aspect of the invention is the use of at least one substituted pyrazoline compound of formula I for which R^1 represents hydrogen, methyl or ethyl, preferably hydrogen for the manufacture of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetes.

ESTA-0423
16.09.2004

Another preferred aspect of the invention is the use of at least one substituted pyrazoline compound of formula wherein the compound of general formula (I) is represented by a compound of general formula (II)



II

wherein

R¹ represents hydrogen or a linear or branched C₁₋₄-alkyl group,

R¹², R¹³, R¹⁴ or R¹⁵ independently of each other represent a linear or branched C₁₋₆-alkyl group, a linear or branched C₁₋₆-alkoxy group, a halogen atom, CH₂F, CHF₂, CF₃, CN, OH, NO₂, SH, NH₂, hydrogen, methyl, ethyl, F, Cl, Br and CF₃,

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof

ESTA-0423
16.09.2004

for the manufacture of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetes.

Another embodiment of the invention is the use of at least one substituted pyrazoline compound of formula II for which R^{12} and R^{13} independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^{12} and R^{13} independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 for the manufacture of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetes.

Another embodiment of the invention is the use of at least one substituted pyrazoline compound of formula II for which R^{14} , and R^{15} independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^{14} and R^{15} independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 for the manufacture of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetes.

Another embodiment of the invention is the use of at least one substituted pyrazoline compound of formula II for which R^{13} represents Cl and R^{12} represents hydrogen for the manufacture of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system

ESTA-0423
16.09.2004

and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetis.

Another preferred embodiment of the invention is the use of at least one substituted pyrazoline compound of formula II for which R^{14} and R^{15} each represent Cl for the manufacture of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetis.

Another preferred embodiment of the invention is the use of at least one substituted pyrazoline compound of formula II for which R^1 represents hydrogen, methyl or ethyl, preferably hydrogen for the manufacture of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetis.

Another embodiment of the invention is the use of at least one substituted pyrazoline compound of formula I or II for which the compound according to formulas I or II is selected from the group consisting of:

5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,

optionally in the form of a corresponding N-oxide, a corresponding salt or a corresponding solvate;

for the manufacture of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of disorders of the

ESTA-0423

16.09.2004

central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetis.

The present invention is illustrated below with the aid of examples. These illustrations are given solely by way of example and do not limit the general spirit of the present invention.

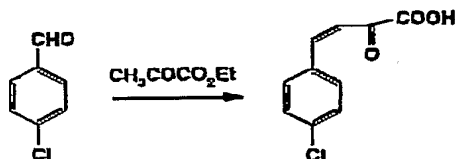
ESTA-0423
16.09.2004

Examples:

Example 0 represent a compound according to formula I or II.

Example 0:

5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-pyrazole-3-carboxylic acid

a) 4-(4-chlorophenyl)-2-oxo-3-butenic acid

In a three neck flask p-chlorobenzaldehyde (13,3 g, 95 mmoles) and ethyl pyruvate (10 g, 86 mmoles) were dissolved in 150 ml of absolute ethanol. The solution was ice-cooled to 0°C and an aqueous solution of NaOH (3.8 g in 45 mL water) was added dropwise keeping the temperature below or equal to 10°C, whereby a yellow-orange colored precipitate was formed. The reaction mixture was stirred for 1 hour at 0°C and an additional 1.5 hours at room temperature (approximately 25 °C). Afterwards the reaction mixture was cooled down to approximately 5°C and the insoluble sodium salt of 4-(4-chlorophenyl)-2-oxo-3-butenic acid was isolated by filtration.

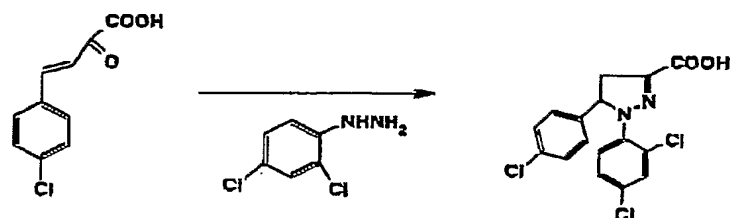
The filtrate was left in the refrigerator overnight, whereby more precipitate is formed, which was filtered off, combined with the first fraction of the salt and washed with diethyl ether. The sodium salt of 4-(4-chlorophenyl)-2-oxo-3-butenic acid was then treated with a solution of 2N HCl, stirred for some minutes and solid 4-(4-chlorophenyl)-2-oxo-3-butenic acid was separated via filtration and dried to give 12.7 g of the desired product (70% of theoretical yield).

IR (KBr, cm⁻¹) : 3500-2500, 1719,3, 1686,5, 1603,4, 1587,8, 1081,9.

¹H NMR(CDCl₃, δ) : 7,4 (d, J=8,4Hz, 2H), 7,5 (d, J=16,1Hz, 1H), 7,6 (d, J=8,4Hz, 2H), 8,1(d, J=16,1Hz, 1H).

ESTA-0423
16.09.2004

b) 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-pyrazole-3-carboxylic acid



4-(4-chlorophenyl)-2-oxo-3-butenoic acid obtained according to step a) (12.6 g, 60 mmol), 2,4-dichlorophenylhydrazine hydrochloride (12.8 g, 60 mmol) and glacial acetic acid (200 mL) were mixed under a nitrogen atmosphere and heated to reflux for 4 hours, cooled down to room temperature (approximately 25 °C) and given into ice-water, whereby a sticky mass was obtained, which was extracted with methylene chloride. The combined methylene chloride fractions were washed with water, dried with sodium sulfate, filtered and evaporated to dryness to give a pale yellow solid (12.7 g, 57% of theoretical yield).

IR (KBr, cm^{-1}) : 3200-2200, 1668,4, 1458, 1251,4, 1104,8.

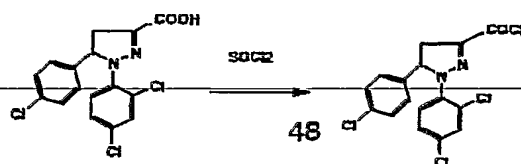
^1H NMR (CDCl_3 , δ) : 3,3 (dd, 1H), 3,7 (dd, 1H), 5,9 (dd, 1H), 7,09-7,25 (m, 7H).

The Examples 1 to 6 represent compounds according to formula X.

Example 1:

N-piperidiny-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazole-3-carboxamide

(a) 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-pyrazole-3-carboxylic acid chloride

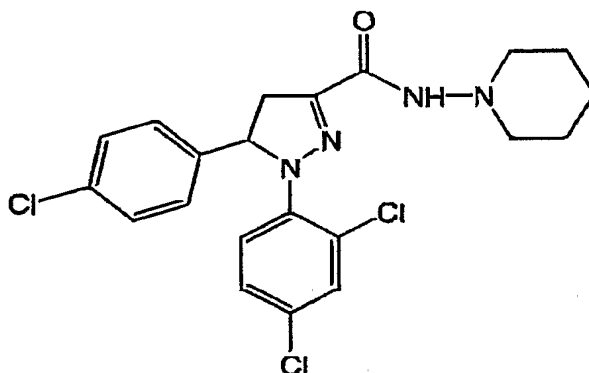


ESTA-0423
16.09.2004

Under nitrogen atmosphere 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-pyrazole-3-carboxylic acid (2.5 g, 6.8 mmols) obtained according to Example 0 was dissolved in 4 mL of thionyl chloride and heated to reflux for 2.5 hours. The excess thionyl chloride is removed from the reaction mixture under reduced pressure and the resulting crude residue (2.6 g) is used without any further purification.

IR (KBr, cm^{-1}) : 1732,3, 1700, 1533,3, 1478,1, 1212,9, 826,6.

(b) N-piperidiny-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydropyrazole-3-carboxamide



Under nitrogen atmosphere N-aminopiperidine (0.6 mL, 5.6 mmols) and triethylamine (4 mL) were dissolved in methylene chloride (25 mL). The resulting mixture was ice-cooled down to 0°C and a solution of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-pyrazole-3-carboxylic acid chloride obtained in step (c) in methylene chloride (15 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature (approximately 25 °C) overnight. Afterwards the reaction mixture was washed with water, followed by a saturated aqueous solution of sodium bicarbonate, then again with water, dried over sodium sulfate, filtered and evaporated to dryness in a rotavapor. The resulting crude solid was crystallized from ethanol.

ESTA-0423
16.09.2004

The crystallized solid was removed via filtration and the mother liquors were concentrated to yield a second fraction of crystallized product. The two fractions were combined to give a total amount of 1.7 g (57% of theoretical yield) of N-piperidinyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydropyrazole-3-carboxamide having a melting point of 183-186°C.

IR (KBr, cm^{-1}) : 3222,9, 2934,9, 1647,4, 1474,7, 1268,3, 815,6.

^1H NMR (CDCl_3 , δ) : 1,4 (m, 2H), 1,7 (m, 4H), 2,8 (m, 4H), 3,3 (dd, $J=6,1$ y $18,3\text{Hz}$, 1H), 3,7 (dd, $J=12,5$ and $18,3\text{ Hz}$, 1H), 5,7 (dd, $J=6,1$ and $12,5\text{ Hz}$, 1H), 7,0-7,2 (m, 6H), 7,4 (s, 1H).

The compounds according to the following examples 2-6 have been prepared analogously to the process described in Example 1 in combination with Example 0.

Example 2:

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid-[1,2,4]triazol-4-yl amide

Melting point: 134-138 °C.

IR (KBr, cm^{-1}): 3448, 1686, 1477, 1243, 1091, 821.

^1H NMR(CDCl_3 , δ): 3,1 (dd, $J=6,2$ and $17,9\text{Hz}$, 1H), 3,7 (dd, $J=12,3$ and $17,9\text{Hz}$, 1H), 5,9 (dd, $J=6,2$ and $12,3\text{ Hz}$, 1H), 7,2-7,5 (m, 7H), 8,7 (s, 2H), 12,0 (bs, 1H).

ESTA-0423
16.09.2004

Example 3:

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid-(4-methyl-piperazin-1-yl)-amide hydrochloride

Melting point: 150-155°C.

IR (KBr, cm^{-1}): 3433, 1685, 1477, 1296, 1246, 1088, 1014, 825.

^1H NMR (CDCl_3 , δ): 2,7 (d, $J=4,2\text{Hz}$, 3H), 3,0-3,4 (m, 9H), 3,6 (dd, $J=11,9$ and $17,9\text{ Hz}$, 1H), 5,8 (dd, $J=5,5$ and $11,9\text{ Hz}$, 1H), 7,1 (d, $J=8,4\text{Hz}$, 2H), 7,25 (2d, $J=8,4$ and $8,7\text{ Hz}$, 3H), 7,4 (d, $J=2,2\text{Hz}$, 1H), 7,5 (d, $J=8,7\text{Hz}$, 1H), 9,8 (s, 1H), 11,2 (bs).

Example 4:

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid diethylamide

This compound was obtained in form of an oil.

IR (film, cm^{-1}): 2974, 1621, 1471, 1274, 1092, 820.

^1H NMR (CDCl_3 , δ): 1,2 (m, 6H), 3,3-3,9 (m, 6H), 5,6 (dd, $J=5,8$ and $11,7\text{ Hz}$, 1H), 7-7,25 (m, 7H).

Example 5:

[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazol-3-yl]-piperidin-1-yl-methanone

Melting point: 105-110°C.

IR (KBr, cm^{-1}): 2934, 1622, 1470, 1446, 1266, 1010, 817.

^1H NMR (CDCl_3 , δ): 1,7 (m, 6H), 3,4 (dd, $J=5,7$ and $17,9\text{Hz}$, 1H), 3,7 (m, 3H), 3,9 (m, 2H), 5,6 (dd, $J=6,1$ y $11,9\text{ Hz}$, 1H), 7-7,25 (m, 7H).

ESTA-0423
16.09.2004

Example 6:

N-[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carbonyl]-4-methyl-phenylsulfonamide

This compound was obtained in form of an amorph solid.

IR (KBr, cm^{-1}): 1697, 1481, 1436, 1340, 1169, 1074, 853.

^1H NMR (CDCl_3 , δ): 2,4 (s, 3H), 3,2 (dd, $J=6,6$ and $18,3\text{Hz}$, 1H), 3,6 (dd, $J=12,8$ and $18,3\text{Hz}$, 1H), 5,8 (dd, $J=6,6$ and $12,8\text{Hz}$, 1H), 7 (d, $J=8,2\text{Hz}$, 2H), 7,2 (s, 1H), 7,3-7,4 (m, 6H), 8 (d, $J=8,1\text{Hz}$, 2H), 9 (s, 1H).

Example 7:

N-oxide of N-piperidiny-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydropyrazole-3-carboxamide

Under nitrogen gas as an inert atmosphere N-piperidiny-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydropyrazole-3-carboxamide (0,15 g, 332 μmoles) was dissolved in 7 ml of dichloromethane. The resulting solution was ice-cooled to 0°C and m-chloroperbenzoic acid (0,204 g, 0,83 μmoles) added in several portions. After stirring for 15 minutes a control via thin layer chromatography showed that no starting material was remaining. A saturated solution of sodium bicarbonate was then slowly added, the organic phase separated, washed with water, dried over sodium sulfate and filtered. The filtered solution was evaporated to dryness and the crude product was purified via column chromatography yielding 78 mg (50 % of theoretical yield) of the N-oxide of N-piperidiny-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydropyrazole-3-carboxamide in form of a white solid having a melting point of $115-120^\circ\text{C}$.

IR (KBr, cm^{-1}): 3202, 1678, 1654, 1474, 1309, 1107.

^1H -NMR (CDCl_3 , δ): 1.6 (m, 2H), 1.8-2.0 (m, 4H), 2.55 (m, 2H), 3.3 (dd, $J = 6.3\text{ Hz}$ and 18.2 Hz , 1H), 3.7 (m, 3H), 5.8 (dd, $J = 6.3\text{ Hz}$ and 12.5 Hz , 1H), 7.0-7.3 (m, 7H), 8.5 (s, 1H.)

ESTA-0423
16.09.2004

Pharmacological Data/Testing:

The compound according to example 0 is an inhibitor of high blood levels of triglycerides. This effect has been probed in obese mice fed with high fat diet. In the following paragraphs it is described the method and the results obtained in this study.

I. In-vivo testing for regulation of triglycerides in blood plasma

The study was done using six weeks old male mice B6 Lep ob/ob, obtained from Charles River (France). Mice were divided in 3 groups : I (control), II (vehicle), III (example 0).

Group I:

The animals of the group I received the standard diet (D-12450B, Research Diets, NJ, USA).

Group II:

The animals of the groups II and III were fed with a High Fat Diet (D-12492, Research Diets, NJ, USA), in both cases for 7 weeks (References 1 and 2).

Group III:

The animals of the groups III were fed with a High Fat Diet (D-12492, Research Diets, NJ, USA), in both cases for 7 weeks (References 1 and 2).

At the end of the feeding period of 7 weeks, it was started the treatment period (14 days): Group II mice received the vehicle (10 ml/kg/day, po, of the aqueous solution of acacia gum, 5% W/V). Group III was administered with 30 mg/kg/day, po, of the inventive compound 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-pyrazole-3-carboxylic acid according to Example 0. Group I didn't received any treatment. The three groups of mice had the same diet than in the previous period.

At the end of the 14 days period of treatment, the blood levels of triglycerides of the animals were determined.

ESTA-0423

16.09.2004

The analysis of the whole blood samples was done using test strips "Lipid panel" and the photometric Analyzer Cardio-Check Test System, from PA Instruments Polymer Technology Systems Indianapolis, IN-46268, USA (Distributed in Spain by Novalab Iberica S.A.L, Madrid, Spain).

The results obtained were the following :

Group	Diet	Treatment	Triglicerides, whole blood levels (mg/dl)	Relative levels
I	Standard	-	61	100%
II	High Fat	Vehicle 10 ml/kg/day po	122.4 (*)	200.6%
III	High Fat	Example 0 30 mg/kg/day po	67.5 (N.S.)	110.6%

(*) : $p < 0.05$, Anova followed Bonferroni t-test, compared with Group I.

NS : Not significant difference, compared with Group I.

The results showed that Group II mice receiving high fat diet had significantly higher triglicerides blood levels than the control Group I. But the administration of the compound according to Example 0 (Group III) improved the triglicerides blood levels, which were not different of the levels of the group I, which received standard diet.

Figure 1 shows the clear reduction of triglyceride levels in blood plasma. The level (Group III) returns to the control level of Group I compared to the clearly raised levels found in the Group II without the treatment with the compound according to Example 0.

Thus, it has been proved the inhibitory effect of the inventive compound 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-pyrazole-3-carboxylic acid according to Example 0. on the high blood levels of triglicerides.

References

ESTA-0423
16.09.2004

1.-Lambert P.D. et al.. "Ciliary neurotrophic factor activates leptin-like pathways and reduces body fat"

P.N.A.S. 2001, 28 (8) : 4652-4657

2.- Grasa M.M. et al "Oleoyl-Estrone lowers the body weight of both ob/ob and db/db mice.

Hozm. Metab. Res 2000, 32 : 246-250

II. In-vivo testing for regulation of triglycerides in blood plasma

In a second set of experiments carried out similar to the tests shown above the TG (triglyceride) levels of diet-induced obese mice in blood were determined.

Mice receiving a high fat diet were - after a feeding period of 6 days - either treated p.o. with vehicle (0,5 % HPMC) or with the compound according to example 0 (30 mg/kg/day p.o.).

TG levels in blood were determined on day 28 after beginning of the treatment.

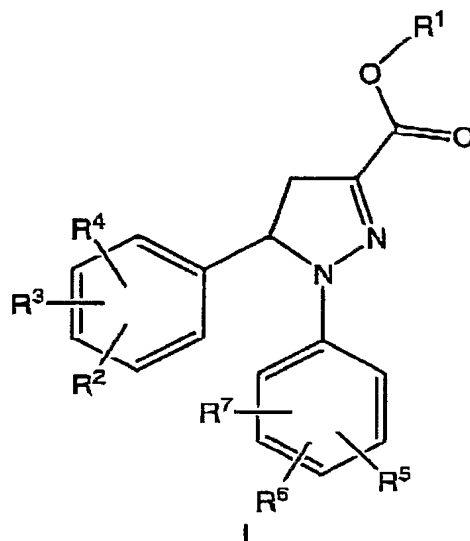
TG (triglyceride) levels were 1.28 ± 25 mmol/l in the group treated with vehicle and only 0.80 ± 0.07 mmol/l in the group treated with the inventive compound 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-pyrazole-3-carboxylic acid according to Example 0. The results were statistically highly significant with an ANOVA factorial, Fisher's post-hoc test of *** $p < 0.005$ vs. vehicle.

Thus, again the inhibitory effect of the inventive compound 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-pyrazole-3-carboxylic acid according to Example 0 on the high blood levels of triglycerides was demonstrated.

ESTA-0423
16.09.2004

Claims:

1. Substituted pyrazoline compounds of general formula I,



wherein

R¹ represents hydrogen or a linear or branched C₁₋₄-alkyl group,

R², R³ and R⁴ independently of each other represent hydrogen, a linear or branched C₁₋₆-alkyl group, a linear or branched C₁₋₆-alkoxy group, a halogen atom, CH₂F, CHF₂, CF₃, CN, OH, NO₂, -(C=O)-R⁸, SH, SR⁸, SOR⁸, SO₂R⁸, NH₂, NHR⁸, NR⁸R⁸, -(C=O)-NH₂, -(C=O)-NHR⁸ or -(C=O)-NR⁸R⁸ whereby R⁸ and R⁹ for each substituent independently represent linear or branched C₁₋₆ alkyl,

R⁵ and R⁶ independently of each other represent a linear or branched C₁₋₆-alkyl group, a linear or branched C₁₋₆-alkoxy group, a halogen atom, CH₂F, CHF₂, CF₃, CN, OH, NO₂, -(C=O)-R¹⁰, SH, SR¹⁰, SOR¹⁰, NH₂, NHR¹⁰, NR¹⁰R¹¹, -(C=O)-NH₂, -(C=O)-NHR¹⁰ and -(C=O)-NR¹⁰R¹¹, whereby R¹⁰ and optionally R¹¹ for each substituent independently represent linear or branched C₁₋₆ alkyl;

ESTA-0423
16.09.2004

R^7 represents hydrogen, a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R^{10}$, SH , SR^{10} , SOR^{10} , NH_2 , NHR^{10} , $NR^{10}R^{11}$, $-(C=O)-NH_2$, $-(C=O)-NHR^{10}$ and $-(C=O)-NR^{10}R^{11}$, whereby R^{10} and optionally R^{11} for each substituent independently represent linear or branched C_{1-8} alkyl;

with the proviso that

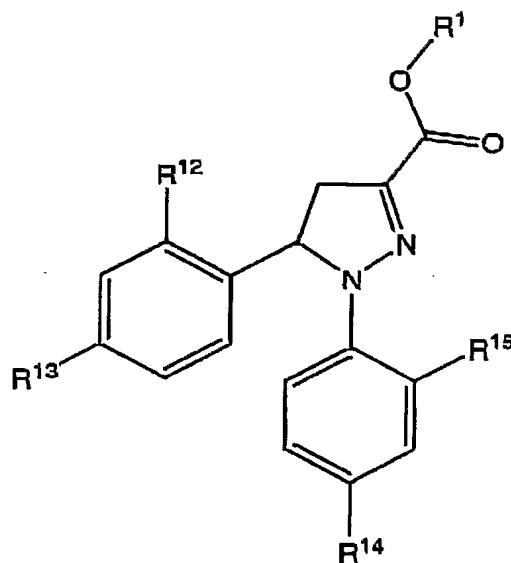
if R^1 and R^7 are H and R^5 and R^8 both represent Cl in the 3- and 4-position of the phenyl ring neither of R^2 , R^3 and R^4 may represent F in the 4-position of the phenyl ring if the other two of R^2 , R^3 and R^4 both represent H;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

2. Compounds according to claim 1, characterized in that at least one of R^2 , R^3 or R^4 represents hydrogen, while at least one of R^2 , R^3 or R^4 is different from hydrogen.
3. Compounds according to any one of claims 1 or 2, characterized in that R^7 represents hydrogen.
4. Compounds according to any one of claims 1 to 3, characterized in that R^2 , R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^2 , R^3 and R^4 independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .
5. Compounds according to any one of claims 1 to 4, characterized in that R^5 and R^8 independently of each other represent a linear or branched C_{1-8} -alkyl group,

ESTA-0423
16.09.2004

- a halogen atom, or CF_3 , preferably R^5 and R^6 independently of each other represent methyl, ethyl, F, Cl, Br and CF_3 .
6. Compounds according to any one of claims 1 to 5, characterized in that R^2 represents a chlorine atom in the 4-position of the phenyl ring, while R^3 and R^4 represent hydrogen.
 7. Compounds according to any one of claims 1 to 6, characterized in that R^5 and R^6 each represent a chlorine atoms in the 2- and 4-position of the phenyl ring, while R^7 represents hydrogen.
 8. Compounds according to any one of claims 1 to 7, characterized in that R^1 represents hydrogen, methyl or ethyl, preferably hydrogen.
 9. Compounds of general formula II according to one or more of claims 1 to 8



II

wherein

R^1 represents hydrogen or a linear or branched C_{1-4} -alkyl group,

ESTA-0423
16.09.2004

R^{12} or R^{13} independently of each other represent a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN, OH, NO_2 , SH, NH_2 , hydrogen, methyl, ethyl, F, Cl, Br and CF_3 ,

R^{14} or R^{15} independently of each other represent a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN, OH, NO_2 , SH, NH_2 , methyl, ethyl, F, Cl, Br and CF_3 ,

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

10. Compounds according to claim 9 characterized in that R^{12} and R^{13} independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^{12} and R^{13} independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .
11. Compounds according to any one of claims 9 or 10, characterized in that R^{14} , and R^{15} independently of each other represent a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^{14} and R^{15} independently of each other represent methyl, ethyl, F, Cl, Br and CF_3 .
12. Compounds according to any one of claims 9 to 11, characterized in that R^{13} represents Cl and R^{12} represents hydrogen.
13. Compounds according to any one of claims 9 to 12, characterized in that R^{14} and R^{15} each represent Cl.
14. Compounds according to any one of claims 9 to 13, characterized in that R^1 represents hydrogen, methyl or ethyl, preferably hydrogen.

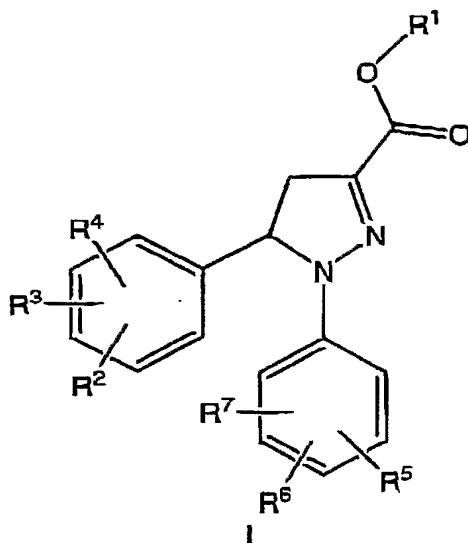
ESTA-0423
16.09.2004

15. Compounds according to one or more of claims 1 to 14 selected from the group consisting of:

5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,

optionally in the form of a corresponding N-oxide, a corresponding salt or a corresponding solvate.

16. Combination of compounds comprising at least one substituted pyrazoline compound of general formula I



wherein

R^1 represents hydrogen or a linear or branched C_{1-4} -alkyl group,

R^2 , R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R^8$, SH , SR^8 , SOR^8 , SO_2R^8 , NH_2 , NHR^8 , NR^8R^9 , $-(C=O)-NH_2$, $-(C=O)-NHR^8$ or $-(C=O)-NR^8R^9$ whereby R^8

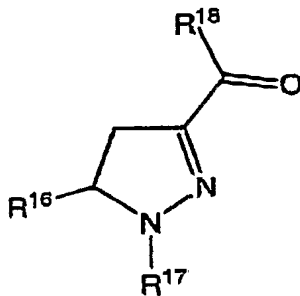
ESTA-0423
16.09.2004

and R^9 for each substituent independently represent linear or branched C_{1-6} alkyl,

R^5 , R^6 and R^7 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R^{10}$, SH , SR^{10} , SOR^{10} , NH_2 , NHR^{10} , $NR^{10}R^{11}$, $-(C=O)-NH_2$, $-(C=O)-NHR^{10}$ and $-(C=O)-NR^{10}R^{11}$, whereby R^{10} and optionally R^{11} for each substituent independently represent linear or branched C_{1-6} alkyl;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof;

and at least one substituted pyrazoline compound of general formula X



X

wherein

R^{16} represents an optionally at least mono-substituted phenyl group,

R^{17} represents an optionally at least mono-substituted phenyl group,

ESTA-0423

16.09.2004

R^{18} represents a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an $-NR^{19}R^{20}$ -moiety,

R^{19} and R^{20} , identical or different, represent a hydrogen atom, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system and/or bonded via a linear or branched alkylene group, an $-SO_2-R^{21}$ -moiety, or an $-NR^{22}R^{23}$ -moiety, with the proviso that R^{19} and R^{20} do not identically represent hydrogen,

R^{21} represents a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic group, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with a mono- or polycyclic ring-system, or an optionally at least mono-substituted aryl or heteroaryl group, which may be condensed with a mono- or polycyclic ring system and/or bonded via a linear or branched alkylene group,

R^{22} and R^{23} , identical or different, represent a hydrogen atom, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least

ESTA-0423
16.09.2004

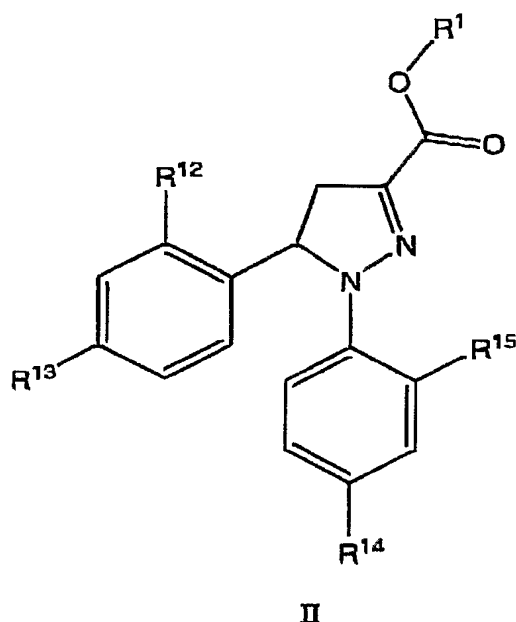
mono-substituted aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system and/or bonded via a linear or branched alkylene group,

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

17. Combination of compounds according to claim 16, characterized in that at least one of R^2 , R^3 or R^4 represents hydrogen, while at least one of R^2 , R^3 or R^4 is different from hydrogen.
18. Combination of compounds according to any one of claims 16 or 17, characterized in that at least one of R^5 , R^6 or R^7 represents hydrogen, while at least one R^5 , R^6 or R^7 is different from hydrogen.
19. Combination of compounds according to any one of claims 16 to 18, characterized in that R^2 , R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^2 , R^3 and R^4 independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .
20. Combination of compounds according to any one of claims 16 to 19, characterized in that R^5 , R^6 and R^7 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^5 , R^6 and R^7 independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .
21. Combination of compounds according to any one of claims 16 to 20, characterized in that R^2 represents a chlorine atom in the 4-position of the phenyl ring, while R^3 and R^4 represent hydrogen.

ESTA-0423
16.09.2004

22. Combination of compounds according to any one of claims 16 to 21, characterized in that R^5 and R^6 each represent a chlorine atoms in the 2- and 4-position of the phenyl ring, while R^7 represents hydrogen.
23. Combination of compounds according to any one of claims 16 to 22, characterized in that R^1 represents hydrogen, methyl or ethyl, preferably hydrogen.
24. Combination of compounds according to any one of claims 16 to 23 characterized in that the compound of general formula I is represented by a compound of general formula II



wherein

R^1 represents hydrogen or a linear or branched C_{1-4} -alkyl group,

R^{12} , R^{13} , R^{14} or R^{15} independently of each other represent a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , SH , NH_2 , hydrogen, methyl, ethyl, F , Cl , Br and CF_3 ,

ESTA-0423
16.09.2004

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

25. Combination of compounds according to claim 24 characterized in that R^{12} and R^{13} independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^{12} and R^{13} independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .
26. Combination of compounds according to any one of claims 24 or 25, characterized in that R^{14} , and R^{15} independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^{14} and R^{15} independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .
27. Combination of compounds according to any one of claims 24 to 26, characterized in that R^{13} represents Cl and R^{12} represents hydrogen.
28. Combination of compounds according to any one of claims 24 to 27, characterized in that R^{14} and R^{15} each represent Cl.
29. Combination of compounds according to any one of claims 24 to 28, characterized in that R^1 represents hydrogen, methyl or ethyl, preferably hydrogen.
30. Combination of compounds according to one or more of claims 16 to 29 characterized in that the compound according to formula I or II selected from the group consisting of:

5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,

ESTA-0423
16.09.2004

optionally in the form of a corresponding N-oxide, a corresponding salt or a corresponding solvate.

31. Combination of compounds according to any of claims 16 to 30, characterized in that R^{16} represents a phenyl group, which is optionally substituted by one or more substituents independently selected from the group consisting of a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R'$, SH , SR' , SOR' , SO_2R' , NH_2 , NHR' , $NR'R''$, $-(C=O)-NH_2$, $-(C=O)-NHR'$ and $-(C=O)-NR'R''$ whereby R' and R'' for each substituent independently represent linear or branched C_{1-6} alkyl, preferably R^{16} represents a phenyl group, which is optionally substituted by one or more substituents selected from the group consisting of methyl, ethyl, F , Cl , Br and CF_3 , more preferably R^{16} represents a phenyl group, which is mono-substituted with a chlorine atom in the 4-position.
32. Combination of compounds according to any of claims 16 to 31, characterized in that R^{17} represents a phenyl group, which is optionally substituted by one or more substituents independently selected from the group consisting of a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R'$, SH , SR' , SOR' , SO_2R' , NH_2 , NHR' , $NR'R''$, $-(C=O)-NH_2$, $-(C=O)-NHR'$ and $-(C=O)-NR'R''$, whereby R' and optionally R'' for each substituent independently represent linear or branched C_{1-6} alkyl, preferably R^{17} represents a phenyl group, which is optionally substituted by one or more substituents independently selected from the group consisting of methyl, ethyl, F , Cl , Br and CF_3 , more preferably R^{17} represents a phenyl group, which is di-substituted with two chlorine atoms in its 2- and 4-position.
33. Combination of compounds according to one or more of claims 16 to 32, characterized in that R^{18} represents a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing C_{3-8} cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an

ESTA-0423
16.09.2004

optionally at least mono-substituted, 5- or 6-membered aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an $-NR^{19}R^{20}$ -moiety, preferably R^{18} represents a saturated, optionally at least mono-substituted, optionally one or more nitrogen-atoms as ring member containing C_{3-8} cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an $-NR^{19}R^{20}$ -moiety, more preferably R^{18} represents a pyrrolidinyl group, a piperidinyl group or a piperazinyl group, whereby each of these groups may be substituted with one or more C_{1-6} -alkyl groups, or an $-NR^{18}R^{19}$ -moiety.

34. Combination of compounds according to one or more of claims 16-33, characterized in that R^{19} and R^{20} , identical or different, represent a hydrogen atom, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted C_{1-6} -aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing C_{3-8} -cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted, 5- or 6-membered aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system and/or bonded via a methylene ($-CH_2-$) or ethylene ($-CH_2-CH_2-$)-group, an $-SO_2R^{21}$ -moiety, or an $-NR^{22}R^{23}$ -moiety, preferably one of these residues R^{19} and R^{20} represents a hydrogen atom and the other one of these residues R^{19} and R^{20} represents a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing C_{3-8} -cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted, 5- or 6-membered aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, an $-SO_2R^{21}$ -moiety, or an $-NR^{22}R^{23}$ -moiety, or R^{19} and R^{20} , identical or different, each represent a C_{1-6} alkyl group, more preferably one of these residues R^{19} and R^{20} represents a hydrogen atom and the other one of these residues R^{19} and R^{20} represents an optionally at least mono-substituted pyrrolidinyl group, an optionally at least

ESTA-0423
16.09.2004

mono-substituted piperidinyl group, an optionally at least mono-substituted piperazinyl group, an optionally at least mono-substituted triazolyl group, an $-SO_2-R^{21}$ -moiety, or an $-NR^{22}R^{23}$ -moiety, or R^{19} and R^{20} , identical or different, represent a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, a sec-butyl group or a tert.-butyl group.

35. Combination of compounds according to one or more of claims 16-34, characterized in that R^{21} represents a linear or branched, saturated or unsaturated, optionally at least mono-substituted C_{1-6} aliphatic group, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing C_{3-8} cycloaliphatic group, which may be condensed with a mono- or polycyclic ring-system, or an optionally at least mono-substituted, 5- or 6-membered aryl or heteroaryl group, which may be condensed with a mono- or polycyclic ring system and/or bonded via a methylene ($-CH_2-$) or ethylene ($-CH_2-CH_2-$)-group, preferably R^{21} represents a C_{1-6} -alkyl group, a saturated, optionally at least mono-substituted cycloaliphatic group, which may be condensed with a mono- or polycyclic ring-system, or a phenyl group, which is optionally substituted with one or more C_{1-6} alkyl groups.
36. Combination of compounds according to one or more of claims 16-35, characterized in that R^{22} and R^{23} , identical or different, represent a hydrogen atom, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted C_{1-6} aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing C_{3-8} cycloaliphatic group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system, or an optionally at least mono-substituted, 5- or 6 membered aryl or heteroaryl group, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring system and/or bonded via a methylene ($-CH_2-$) or ethylene ($-CH_2-CH_2-$)-group, preferably R^{22} and R^{23} , identical or different, represent a hydrogen atom or a C_{1-6} alkyl radical.

ESTA-0423
16.09.2004

37. Combination of compounds according to any of claims 16 to 36 characterized in that the compound according to general formula X is represented by a structure wherein

R^{16} represents a phenyl ring, which is mono-substituted with a halogen atom, preferably a chlorine atom, in its 4-position,

R^{17} represents a phenyl ring, which is di-substituted with two halogen atoms, preferably chlorine atoms, in its 2- and 4-position,

R^{18} represents a pyrrolidinyl group, a piperidinyl group, a piperazinyl group, a homo-piperazinyl group, a morpholinyl group, or an $-NR^{19}R^{20}$ -moiety,

R^{19} represents a hydrogen atom or a linear or branched C_{1-6} -alkyl group,

R^{20} represents a linear or branched C_{1-6} alkyl group, an $-SO_2-R^{21}$ -moiety, a pyrrolidinyl group, a piperidinyl group, a piperazinyl group, a homo-piperazinyl group, a morpholinyl group, a triazolyl group, whereby each of the heterocyclic rings may be substituted with one or more, identical or different, C_{1-6} -alkyl groups, and

R^{21} represents a phenyl group, which is optionally substituted with one or more C_{1-6} alkyl groups, which may be identical or different,

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

38. Combination of compounds according to one or more of claims 16 to 37, characterized in that it comprises at least one compound according to formula X selected from the group consisting of:

ESTA-0423
16.09.2004

N-piperidiny-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxamide,

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid-[1,2,4]-triazole-4-yl-amide,

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid-(4-methyl-piperazin-1-yl)-amide,

5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylic acid diethylamide,

[5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4,5-dihydro-1H-pyrazole-3-yl]-piperidine-1-yl-methanone,

N-[5-(4-Chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazole-3-carbonyl]-4-methylphenylsulfonamide,

optionally in the form of a corresponding N-oxide, a corresponding salt or a corresponding solvate.

39. Combination of compounds according to one or more of claims 16 to 38, characterized in that it comprises at least

5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,

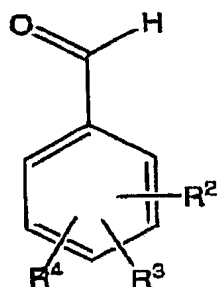
and

N-piperidiny-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxamide;

each optionally in the form of a corresponding N-oxide, a corresponding salt or a corresponding solvate.

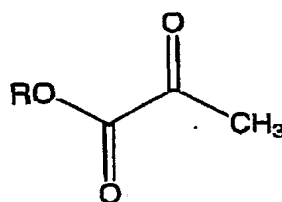
ESTA-0423
16.09.2004

40. Process for the manufacture of substituted pyrazoline compounds of general formula I or II according to one or more of claims 1 to 15, characterized in that at least one benzaldehyde compound of general formula III



(III)

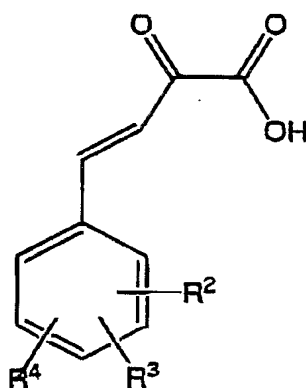
wherein R^2 , R^3 and R^4 have the meaning according to one or more of claims 1-8, is reacted with a pyruvate compound of general formula (IV)



(IV),

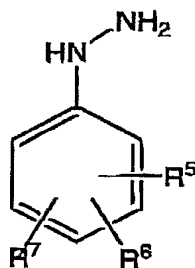
wherein R is a branched or unbranched C_{1-6} alkyl radical, to yield a compound of general formula (V)

ESTA-0423
16.09.2004



(V)

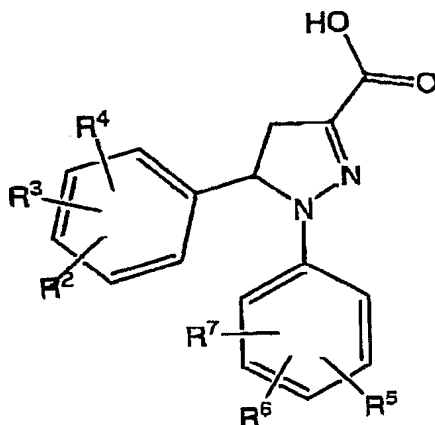
wherein R^1 has the meaning given above, which is optionally isolated and/or optionally purified, and which is reacted with an optionally substituted phenyl hydrazine of general formula (VI)



(VI)

or a corresponding salt thereof, wherein R^5 , R^6 and R^7 have the meaning according to one or more of claims 1-8, under inert atmosphere, to yield a compound of general formula (VII)

ESTA-0423
16.09.2004

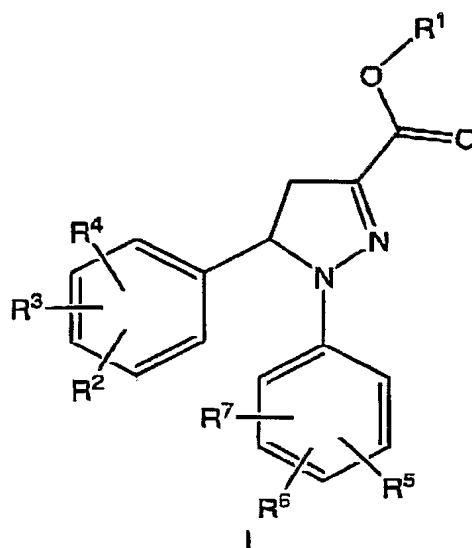


(VII)

wherein R², R³, R⁴, R⁵, R⁶ and R⁷ have the meaning as given above, which is optionally isolated and/or optionally purified, and optionally esterified to an alkyl-ester if in the substituted pyrazoline compound of general formula I according to one or more of claims 1 to 15 R¹ is a linear or branched C₁₋₄-alkyl group.

41. Medicament comprising at least one substituted pyrazoline compound of general formula I or II according to one or more of claims 1 to 15, and optionally one or more pharmaceutically acceptable excipients.
42. Medicament comprising at least one substituted pyrazoline compound of general formula I

ESTA-0423
16.09.2004



wherein

R^1 represents hydrogen or a linear or branched C_{1-4} -alkyl group,

R^2 , R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R^8$, SH , SR^8 , SOR^8 , SO_2R^8 , NH_2 , NHR^8 , NR^8R^9 , $-(C=O)-NH_2$, $-(C=O)-NHR^8$ or $-(C=O)-NR^8R^9$ whereby R^8 and R^9 for each substituent independently represent linear or branched C_{1-6} alkyl,

R^5 , R^6 and R^7 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R^{10}$, SH , SR^{10} , SOR^{10} , NH_2 , NHR^{10} , $NR^{10}R^{11}$, $-(C=O)-NH_2$, $-(C=O)-NHR^{10}$ and $-(C=O)-NR^{10}R^{11}$, whereby R^{10} and optionally R^{11} for each substituent independently represent linear or branched C_{1-6} alkyl;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the

ESTA-0423
16.09.2004

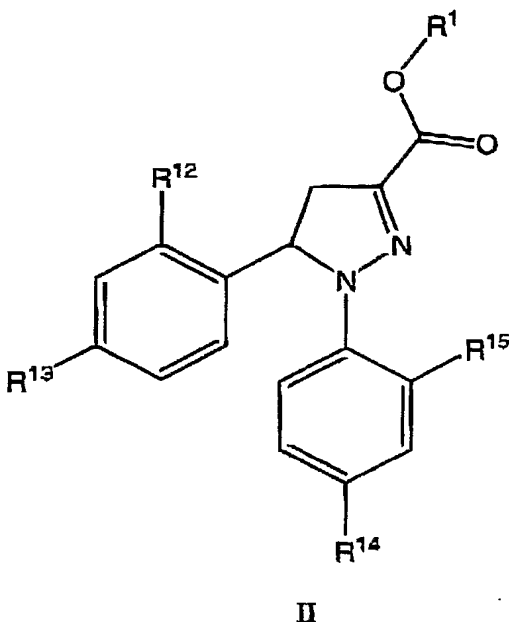
stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof;

and optionally one or more pharmaceutically acceptable excipients.

43. Medicament according to claim 42, characterized in that at least one of R^2 , R^3 or R^4 represents hydrogen, while at least one of R^2 , R^3 or R^4 is different from hydrogen.
44. Medicament according to any one of claims 42 or 43, characterized in that at least one of R^5 , R^6 or R^7 represents hydrogen, while at least one R^5 , R^6 or R^7 is different from hydrogen.
45. Medicament according to any one of claims 42 to 44, characterized in that R^2 , R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^2 , R^3 and R^4 independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .
46. Medicament according to any one of claims 42 to 45, characterized in that R^5 , R^6 and R^7 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^5 , R^6 and R^7 independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .
47. Medicament according to any one of claims 42 to 46, characterized in that R^2 represents a chlorine atom in the 4-position of the phenyl ring, while R^3 and R^4 represent hydrogen.
48. Medicament according to any one of claims 42 to 47, characterized in that R^5 and R^6 each represent a chlorine atom in the 2- and 4-position of the phenyl ring, while R^7 represents hydrogen.

ESTA-0423
16.09.2004

49. Medicament according to any one of claims 42 to 48, characterized in that R^1 represents hydrogen, methyl or ethyl, preferably hydrogen.
50. Medicament according to one or more of claims 42 to 49 characterized in that the compound of general formula (I) is represented by a compound of general formula (II)



wherein

R^1 represents hydrogen or a linear or branched C_{1-4} -alkyl group,

R^{12} , R^{13} , R^{14} or R^{15} independently of each other represent a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , SH , NH_2 , hydrogen, methyl, ethyl, F , Cl , Br and CF_3 ,

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing

ESTA-0423
16.09.2004

ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

51. Medicament according to claim 50 characterized in that R^{12} and R^{13} independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^{12} and R^{13} independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .
52. Medicament according to any one of claims 50 or 51, characterized in that R^{14} , and R^{15} independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^{14} and R^{15} independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .
53. Medicament according to any one of claims 50 to 52, characterized in that R^{13} represents Cl and R^{12} represents hydrogen.
54. Medicament according to any one of claims 50 to 53, characterized in that R^{14} and R^{15} each represent Cl.
55. Medicament according to any one of claims 50 to 54, characterized in that R^1 represents hydrogen, methyl or ethyl, preferably hydrogen.
56. Medicament according to one or more of claims 42 to 55 characterized in that the compound according to formulas I or II is selected from the group consisting of:

5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,

optionally in the form of a corresponding N-oxide, a corresponding salt or a corresponding solvate.

ESTA-0423
16.09.2004

57. Medicament comprising at least one combination of compounds according to one or more of claims 16 to 39 and optionally one or more pharmaceutically acceptable excipients.
58. Medicament according to claim 42 to 57 for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, preferably bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetes.
59. Medicament according to one or more of claims 42 to 56 for the prophylaxis and/or treatment of disorders of the central nervous system, disorders of the immune system, disorders of the cardiovascular system, disorders of the endocrinous system, disorders of the respiratory system, disorders of the gastrointestinal tract or reproductive disorders.
60. Medicament according to claim 57 for the modulation of cannabinoid-receptors, preferably cannabinoid 1 (CB₁) receptors, for the prophylaxis and/or treatment of disorders of the central nervous system, disorders of the immune system, disorders of the cardiovascular system, disorders of the endocrinous system, disorders of the respiratory system, disorders of the gastrointestinal tract or reproductive disorders.
61. Medicament according to one or more of claims 42 to 57 for the prophylaxis and/or treatment of food intake disorders, preferably bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity.
62. Medicament according to one or more of claims 42 to 57 for the prophylaxis and/or treatment of psychosis.
63. Medicament according to one or more of claims 42 to 57 for the prophylaxis and/or treatment of alcohol abuse and/or addiction, nicotine abuse and/or

ESTA-0423
16.09.2004

addiction, drug abuse and/or addiction and/or medicament abuse and/or addiction, preferably drug abuse and/or addiction and/or nicotine abuse and/or addiction.

64. Medicament according to one or more of claims 42 to 57 for the prophylaxis and/or treatment of one or more disorders selected from the group consisting of schizophrenia, anxiety, depression, epilepsy, neurodegenerative disorders, cerebellar disorders, spinocerebellar disorders, cognitive disorders, cranial trauma, panic attacks, peripheral neuropathy, glaucoma, migraine, Morbus Parkinson, Morbus Huntington, Morbus Alzheimer, Raynaud's disease, tremblement disorders, compulsive disorders, senile dementia, thymic disorders, tardive dyskinesia, bipolar disorders, cancer, medicament-induced movement disorders, dystonia, endotoxemic shock, hemorrhagic shock, hypotension, insomnia, immunologic disorders, sclerotic plaques, vomiting, diarrhea, asthma, memory disorders, pruritus, pain, or for potentiation of the analgesic effect of narcotic and non-narcotic analgesics, or for influencing intestinal transit.
65. Use of at least one substituted pyrazoline compound according to one or more of claims 1 - 15 or at least one combination of compounds according to one or more of claims 16 to 39 and optionally one or more pharmaceutically acceptable excipients, for the preparation of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetes.
66. Use of at least one substituted pyrazoline compound according to one or more of claims 1 - 15 and optionally one or more pharmaceutically acceptable excipients, for the preparation of a medicament for the prophylaxis and/or treatment of disorders of the central nervous system, disorders of the immune system, disorders of the cardiovascular system, disorders of the endocrinous

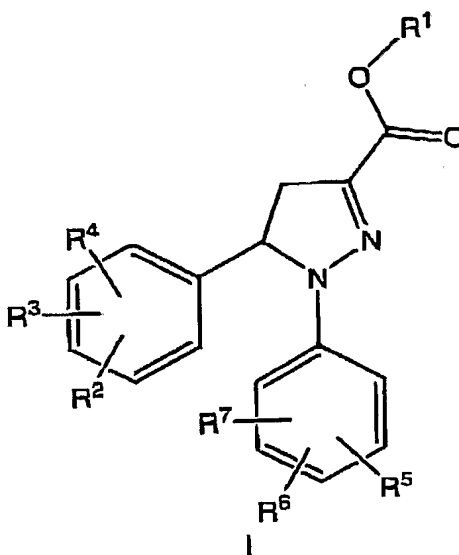
ESTA-0423
16.09.2004

system, disorders of the respiratory system, disorders of the gastrointestinal tract or reproductive disorders.

67. Use of at least one combination of compounds according to one or more of claims 16 to 39 and optionally one or more pharmaceutically acceptable excipients, for the preparation of a medicament for the modulation of cannabinoid-receptors, preferably cannabinoid 1 (CB₁) receptors, for the prophylaxis and/or treatment of disorders of the central nervous system, disorders of the immune system, disorders of the cardiovascular system, disorders of the endocrinous system, disorders of the respiratory system, disorders of the gastrointestinal tract or reproductive disorders.
68. Use of at least one substituted pyrazoline compound according to one or more of claims 1-15 or at least one combination of compounds according to one or more of claims 16 to 39 and optionally one or more pharmaceutically acceptable excipients, for the preparation of a medicament for the prophylaxis and/or treatment of food intake disorders, preferably bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity.
69. Use of at least one substituted pyrazoline compound according to one or more of claims 1-15 or at least one combination of compounds according to one or more of claims 16 to 39 and optionally one or more pharmaceutically acceptable excipients, for the preparation of a medicament for the prophylaxis and/or treatment of psychosis.
70. Use of at least one substituted pyrazoline compound according to one or more of claims 1-15 or at least one combination of compounds according to one or more of claims 16 to 39 and optionally one or more pharmaceutically acceptable excipients, for the preparation of a medicament for the prophylaxis and/or treatment of alcohol abuse and/or addiction, nicotine abuse and/or addiction, medicament abuse and/or addiction and/or drug abuse and/or addiction, preferably drug abuse and/or addiction or nicotine abuse and/or addiction.

ESTA-0423
16.09.2004

71. Use of at least one substituted pyrazoline compound according to one or more of claims 1-15 or at least one combination of compounds according to one or more of claims 16 to 39 and optionally one or more pharmaceutically acceptable excipients, for the preparation of a medicament for the prophylaxis and/or treatment of one or more disorders selected from the group consisting of schizophrenia, anxiety, depression, epilepsy, neurodegenerative disorders, cerebellar disorders, spinocerebellar disorders, cognitive disorders, cranial trauma, panic attacks, peripheric neuropathy, glaucoma, migraine, Morbus Parkinson, Morbus Huntington, Morbus Alzheimer, Raynaud's disease, tremblement disorders, compulsive disorders, senile dementia, thymic disorders, tardive dyskinesia, bipolar disorders, cancer, medicament-induced movement disorders, dystonia, endotoxemic shock, hemorrhagic shock, hypotension, insomnia, immunologic disorders, sclerotic plaques, vomiting, diarrhea, asthma, memory disorders, pruritus, pain, or for potentiation of the analgesic effect of narcotic and non-narcotic analgesics, or for influencing intestinal transit.
72. Use of at least one substituted pyrazoline compound of general formula I



ESTA-0423
16.09.2004

wherein

R^1 represents hydrogen or a linear or branched C_{1-4} -alkyl group,

R^2 , R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R^8$, SH , SR^8 , SOR^8 , SO_2R^8 , NH_2 , NHR^8 , NR^8R^9 , $-(C=O)-NH_2$, $-(C=O)-NHR^8$ or $-(C=O)-NR^8R^9$ whereby R^8 and R^9 for each substituent independently represent linear or branched C_{1-6} alkyl,

R^5 , R^6 and R^7 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a linear or branched C_{1-6} -alkoxy group, a halogen atom, CH_2F , CHF_2 , CF_3 , CN , OH , NO_2 , $-(C=O)-R^{10}$, SH , SR^{10} , SOR^{10} , NH_2 , NHR^{10} , $NR^{10}R^{11}$, $-(C=O)-NH_2$, $-(C=O)-NHR^{10}$ and $-(C=O)-NR^{10}R^{11}$, whereby R^{10} and optionally R^{11} for each substituent independently represent linear or branched C_{1-6} alkyl;

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof;

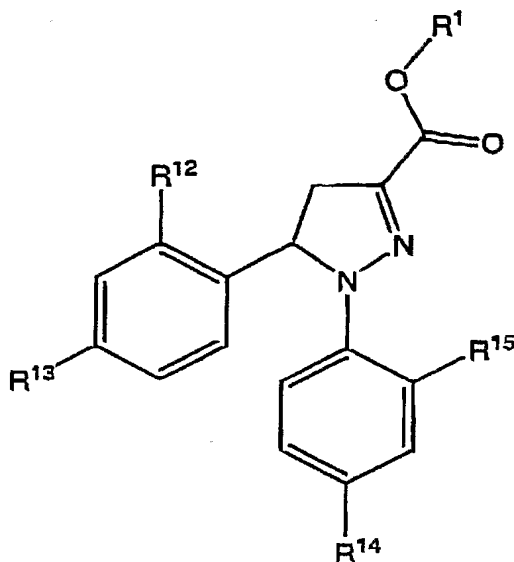
and optionally one or more pharmaceutically acceptable excipients, for the preparation of a medicament for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of food intake disorders, especially bulimia, anorexia, cachexia, obesity, type II diabetes mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetes.

ESTA-0429
16.09.2004

73. Use according to claim 72, characterized in that at least one of R^2 , R^3 or R^4 represents hydrogen, while at least one of R^2 , R^3 or R^4 is different from hydrogen.
74. Use according to any one of claims 72 or 73, characterized in that at least one of R^5 , R^6 or R^7 represents hydrogen, while at least one R^5 , R^6 or R^7 is different from hydrogen.
75. Use according to any one of claims 72 to 74, characterized in that R^2 , R^3 and R^4 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^2 , R^3 and R^4 independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .
76. Use according to any one of claims 72 to 75, characterized in that R^5 , R^6 and R^7 independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^5 , R^6 and R^7 independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .
77. Use according to any one of claims 72 to 76, characterized in that R^2 represents a chlorine atom in the 4-position of the phenyl ring, while R^3 and R^4 represent hydrogen.
78. Use according to any one of claims 72 to 77, characterized in that R^5 and R^6 each represent a chlorine atom in the 2- and 4-position of the phenyl ring, while R^7 represents hydrogen.
79. Use according to any one of claims 72 to 78, characterized in that R^1 represents hydrogen, methyl or ethyl, preferably hydrogen.

ESTA-0423
16.09.2004

80. Use according to one or more of claims 72 to 79 characterized in that the compound of general formula (I) is represented by a compound of general formula (II)



II

wherein

R¹ represents hydrogen or a linear or branched C₁₋₄-alkyl group,

R¹², R¹³, R¹⁴ or R¹⁵ independently of each other represent a linear or branched C₁₋₈-alkyl group, a linear or branched C₁₋₈-alkoxy group, a halogen atom, CH₂F, CHF₂, CF₃, CN, OH, NO₂, SH, NH₂, hydrogen, methyl, ethyl, F, Cl, Br and CF₃,

optionally in form of one of the stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of the stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a corresponding N-oxide thereof, or a corresponding salt thereof, or a corresponding solvate thereof.

ESTA-0423

16.09.2004

81. Use according to claim 80 characterized in that R^{12} and R^{13} independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^{12} and R^{13} independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .
82. Use according to any one of claims 80 or 81, characterized in that R^{14} , and R^{15} independently of each other represent hydrogen, a linear or branched C_{1-6} -alkyl group, a halogen atom, or CF_3 , preferably R^{14} and R^{15} independently of each other represent hydrogen, methyl, ethyl, F, Cl, Br and CF_3 .
83. Use according to any one of claims 80 to 82, characterized in that R^{13} represents Cl and R^{12} represents hydrogen.
84. Use according to any one of claims 80 to 83, characterized in that R^{14} and R^{15} each represent Cl.
85. Use according to any one of claims 80 to 84, characterized in that R^1 represents hydrogen, methyl or ethyl, preferably hydrogen.
86. Use according to one or more of claims 72 to 85 characterized in that the compound according to formulas I or II is selected from the group consisting of:

5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-carboxylic acid,

optionally in the form of a corresponding N-oxide, a corresponding salt or a corresponding solvate.

ESTA-0423
16.09.2004

Abstract

The present invention relates to substituted pyrazoline compounds, methods for their preparation, medicaments comprising these compounds as well as their use for the preparation of a medicament for the treatment of humans and animal.

Fig. 1)
Effects of the compound according to example 0 on the level of triglycerides in the blood
plasma of mice ob/ob



